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A CHALLENGE TO CANADIAN ANAESTHESIA

IT IS EVIDENT that this is an opportune time to establish well-considered plans for the future of Canadian anaesthesia.

Across the country, dedicated men, as members of hospital boards and medical staffs, are devoting time and study towards providing the best possible hospital facilities for all communities. In large teaching hospitals, highly specialized services are being developed. Peripheral hospitals are mushrooming around large metropolitan centres, and every rural community with a population of 5,000 or more will soon have an institution for the local care of the sick.

Well-trained young surgeons are becoming established in smaller cities. These young men require a standard of anaesthesia services not always available.

It is unfortunately true that the average recently qualified young physician, at the time he finishes his rotating internship, is not adequately qualified to function as an anaesthetist on the staff of a hospital.

Senior anaesthetists in teaching centres receive frequent requests from hospital authorities and from surgeons for assistance in the provision of more efficient and progressive anaesthesia for their institutions. All seem to offer adequate opportunities and income, but too often the right man is not available.

Our present system is producing an adequate number of qualified anaesthetists to fill available vacancies in larger institutions, and teaching hospitals. However, a substantial part of our large rural population is cared for in community hospitals. Many of these institutions are at present functioning without the assistance of physicians with special training in anaesthesia.

The Royal College of Physicians and Surgeons of Canada has already established an excellent standard for senior status. Young men with these qualifications will provide versatile and competent professional care, contribute adequately to the development of specialized services and teach the undergraduate and postgraduate students.

For some years to come, however, men with such advanced training will not be available in sufficient numbers to meet the requirements of community hospitals. These institutions will continue to refer their specialized problems elsewhere. They will need competent men with good general training and ability to meet the local needs related to anaesthesia for general, traumatic, and paediatric surgery and obstetrics and gynaecology. For this service, the academic requirements need not be as advanced as for senior teaching and consultant posts.

It, therefore, seems reasonable to consider the future establishment of a junior qualification on a provincial level. It would not compete but would be integrated with the presently revised Royal College requirements to be established in 1965.

If we will indulge in a bit of honest self-criticism, we will admit that we are not attracting an adequate number of bright young Canadian doctors for the future requirements of our specialty. Present stipends do not provide a reasonable standard of living for the young married man in training. After having endured poverty for seven or eight years, the professional motivations of the young graduate are considerably dulled by the prospect of the additional four or five years of penury required to become a specialist.

With improved economic arrangements, and a better integrated system for progressive training, the potentialities would be more attractive. To demand four years of continuous training for the junior group would be unrealistic. Properly organized programmes can produce good anaesthetists in less time. Such an arrangement would provide the interested interne with opportunities to train for a junior appointment in a large hospital or service in a smaller hospital, and he could later advance to fellowship status.

Presently established part-time anaesthetists could leave for further training without too much sacrifice and return with improved ability to contribute to their community.

Competent young men unable to acquire fellowship status, for either economic or academic reasons, would be spared to accept appointments with less demanding professional and teaching responsibilities.

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UN DEFI A L'ANESTHESIE CANADIENNE

SELON TOUTE ÉVIDENCE c'est le temps opportun de fixer des cadres bien étudiés pour l'avenir de l'anesthésie canadienne.

D'un bout à l'autre du pays, des hommes dévoués, en qualité de membres du bureau des gouverneurs d'un hôpital ou en qualité de membres des bureaux médicaux, étudient et dépensent leur temps pour essayer de procurer à tous les groupes de citoyens les plus grandes facilités hospitalières possibles. On a constitué, dans les grands hôpitaux enseignants, des services hautement spécialisés. Autour des grands centres métropolitains, des hôpitaux de province poussent comme des champignons et chaque petit groupe rural d'une population de 5,000 habitants et plus aura bientôt une institution pour prendre soin des malades qui s'y rencontrent.

Des chirurgiens bien entraînés se dirigent maintenant vers des villes moins populeuses pour y pratiquer leur profession. Ces jeunes gens exigent des services d'anesthésie d'une capacité scientifique moyenne ce qu'ils ne peuvent pas toujours obtenir.

Il est malheureusement vrai que, parmi les récents gradués, la plupart, au moment où ils finissent leur rotation comme interne, ne possèdent pas les qualifications requises pour agir comme anesthésiste dans un hôpital.

Fréquemment, les anesthésistes des centres d'enseignement reçoivent, soit des autorités hospitalières, soit des chirurgiens de ces hôpitaux de province, des demandes d'aide pour assurer, dans leur institution, une anesthésie plus efficace et plus progressive. Tous semblent offrir un poste et un revenu acceptables mais, bien souvent, on ne peut pas trouver l'homme désirable pour accepter ce poste.

Le Collège Royal des Médecins et Chirurgiens du Canada a déjà établi un excellent filtre pour la classification des seniors. Les jeunes gens qui possèdent les qualifications pour ce titre sont capables de donner des soins professionnels des plus compétents et des plus variés, de faire leur part pour établir des services d'anesthésie spécialisés et de faire de l'enseignement aussi bien aux membres du cours universitaire qu'à ceux du cours post-universitaire.

Toutefois, pour quelques années à venir, on ne pourra pas rencontrer ces hommes hautement qualifiés en nombre suffisant pour répondre aux demandes des hôpitaux de province. Ces hôpitaux devront continuer à diriger ailleurs leurs cas problèmes. Ils auront besoin d'hommes compétents avec un bon entraînement général et une grande habilité pour satisfaire aux besoins locaux en anesthésie: pour rendre possible la chirurgie générale traumatique et pédiatrique ainsi que la gynécologie et l'obstétrique. Pour remplir ces fonctions, il n'est pas nécessaire que les exigences académiques soient aussi grandes que pour remplir les postes de consultants et de professeurs.

En conséquence, il semblerait raisonnable d'étudier les possibilités de fixer, sur une échelle provinciale, les exigences d'une qualification inférieure. Cette classification n'irait pas à l'encontre mais, au contraire, entrerait dans le cadre revisé des exigences du Collège Royal, cadre qui sera établi en 1965.

En toute sincérité et honnête auto-critique, il nous faut avouer que nous ne réussissons pas à attirer un nombre suffisant de jeunes brillants docteurs canadiens pour répondre aux exigences de notre spécialité. Les salaires actuels ne sont pas suffisants pour procurer à un jeune homme marié, à l'entraînement, des conditions de vie convenables. Après avoir supporté la pauvreté pendant sept ou huit ans, le jeune gradué voit ses ambitions professionnelles assez fortement inhibées par la perspective, s'il désire se spécialiser, de quatre ou cinq années additionnelles de rationnement sinon de pénurie.

Si nous pouvions améliorer la situation économique et trouver un meilleur système d'entraînement progressif, les perspectives d'avenir seraient plus attrayantes. Exiger quatre années d'entraînement continuel pour ce groupe junior ne serait pas faire preuve de réalisme. Des programmes bien organisés peuvent, en moins de temps, former de bons anesthésistes. Une organisation semblable pourrait offrir à l'interne intéressé des chances de se qualifier pour un titre de junior dans un grand hôpital ou pour un service dans un hôpital plus petit et, plus tard, il pourrait atteindre les qualifications du titre d'Associé.

Les anesthésistes à temps partiel qui existent actuellement pourraient s'absenter sans trop de sacrifices pour compléter leur entraînement et retourner ensuite dans leur localité avec des qualifications supérieures et une plus grande habileté.

Parmi ces jeunes gens compétents, ceux qui, pour des raisons économiques ou académiques, ne peuvent obtenir les qualifications du titre d'Associé, pourraient remplir des postes où l'on demande moins d'enseignement et moins de responsabilités professionnelles.

ALAN B. NOBLE, M.D.

THE DEVELOPMENT OF THE CONCEPT OF HYPOXIA-ANOXIA[1,2]

CYRIL B. COURVILLE, M.D.[3]

IT MATTERS LITTLE what field of medicine one wishes to explore from the viewpoint of history; the development of knowledge about it seems to follow a similar pattern. At first, only the most obvious features of a natural phenomenon are noted, such as would be apparent to the average lay mind. Then some simple deduction as to the significance of this phenomenon is made and verified until it becomes a part of current knowledge. Other observations which emphasize different features of the concept are then slowly added to this store of information until the crude outlines of the subject can be distinguished. After printing was invented, this process accelerated since general observations could be put under the scrutiny of many individuals. Experimentation finally subjects these concepts to critical test so that the fundamentals of scientific thought are finally worked out. This evolution of thought about any natural phenomenon is a very slow process, requiring thousands of years even for the rudiments of an idea to become well known.

The historical development of knowledge of the significance of respiration in its relation to the effects of oxygen-want on the nervous system follows this pattern, as will be briefly outlined herein.

Prehistoric man undoubtedly experienced difficulty in breathing when exposed to the smoke of his cave campfires; certainly he occasionally suffered from laryngeal obstruction from a hastily gulped bolus of meat, or nearly drowned in the lakes whose borders he dared trespass. However, if he had any ideas about the absolute necessity of respiration to life, we have no way of knowing it. Hence, any attempt to trace, from the beginnings of things to the present, the *concept* of impaired respiration in its broadest sense, is to undertake the impossible. The writer will be forgiven, he hopes, if this historical approach to the human conception of oxygen-want proves to be rather sketchy. Yet it may be profitable to trace its tenuous course throughout a period of four thousand years or more.

ANOXIA IN ANCIENT TIMES

There is direct evidence that prehistoric man occasionally suffered from the effects of oxygen-want to the point of his individual extinction. This is suggested

[1]Presented at the meeting of the Western Divisions, Canadian Anaesthetists' Society, at Victoria, B.C., April 28–30, 1960.

[2]In order to avoid confusion, the terms hypoxia and anoxia are used in the sense suggested by Wiggers (1). Accordingly, hypoxia implies a lowered oxygen tension in the blood with evident physiological changes which are reversible leading to complete normalcy; anoxia indicates a state of oxygen lack to a degree resulting in pathological alterations in the brain resulting in fatal issue or physical and/or mental deficits during the survival period.

[3]From the Division of Nervous Diseases (Neurology), College of Medical Evangelists, and the Cajal Laboratory of Neuropathology, Los Angeles County Hospital, Los Angeles, Calif.

by the discovery of a skeleton found buried in the shaft of a flint mine at Obourg, Belgium. Three other skeletons were discovered under a landslide at La Ferrassie, France. All these individuals had evidently been suffocated by being suddenly covered with earth. Less dramatic were the effects of respiratory embarrassment from breathing of rarefied atmosphere. Aristotle (384–322 B.C.) probably referred to a common experience when he complained that the air on Mount Olympus was too thin for respiration. More significant are the stories of drowning in ancient times in which many individuals came to their end. According to Pliny and Celsus, drowning was considered to be a form of suffocation, a concept which was widely accepted throughout the Middle Ages and Renaissance (for example, Sylvius, 1635). A study on the cause of death in drowning was instituted by Nachtigal (1775–6), bringing this problem well up to recent times.

Mechanical strangulation, both accidental and purposeful, has also been known from ancient times, being used by the Assyrians and the Babylonians either for capital punishment or for the destruction of prisoners of war. While this mode of exitus was recognized in Biblical times as a horrible way to die (Job 7:15), it is not known what was thought to be the mechanism of the victim's death. That this form of asphyxia was recognized as an interference with respiration was suggested by the methods of execution used by the Chinese of the late dynastic period. The upper air passages of the victims were plugged solid with wads of paper soaked in spirits. This is also indicated by the common practice of infanticide in the Middle Ages when mothers rid themselves of unwanted infants by pressing their mouths against the mattress of their cribs.

Anoxia and Foreign Gases

Thus the stage was set for the idea that air was a necessity of life and that a sufficient amount of it must have access to the lungs at all times. If the air was "too thin" or if there was any mechanical obstruction to its entrance to the lungs, severe distress occurred which was sometimes followed by death. This was perhaps the first accepted concept with respect to hypoxia. The second important concept seemed to follow naturally, that is, when any vapour or gas replaced the air, symptoms similar to suffocation would occur.

Somewhat akin to our present understanding of the relation of nitrous oxide to anoxia was the observation of asphyxiation incident to certain noxious gases. This was presumably a common cause of death among the slave miners of Egypt and laborers in the silver-lead mines of Greece. It is difficult to be certain, however, that the Greeks were actually aware of the precise cause of death in these cases. The fact that fires were kept burning in the tunnels and shafts of these mines suggests the suspicion that stagnation of air was indeed responsible. The first indication that this situation was correctly understood was a statement of Vitruvius (first century A.D.) to the effect that death in the mines could follow inhalation of noxious vapours. He advocated that a lighted lamp be introduced into the shaft before the miner descended into it. If the light continued to burn, the shaft was considered safe. Whether contemporary mediaeval physicians went a step further and recognized the necessity of some normal constituent of air in

order to prevent such catastrophies is uncertain. It is safe to say, however, that Galen (A.D. 131–201) was the first physician to call attention to the suffocating effect of extraneous fumes in the copper mines of Cyprus. This appreciation probably marks the earliest concept of asphyxiation by a replacement of normal constituents of air by some other gaseous substance. Such a conclusion was supported centuries later by the observations of Agricola (1556), a mining engineer, who observed that the presence of such gases was the cause of difficulty of respiration, a symptom which sometimes resulted in actual suffocation. In the eighteenth and nineteenth centuries, it was recognized that these noxious gases constituted a foreign element in the air and that they occurred most abundantly in coal mines.

Early in the Christian era, it was reported that accidents sometimes followed inhalation of fumes from burning charcoal. Erasistratus (*ca.* 300 B.C.) had suspected even at this early date that the vapours issuing from the heated charcoal somehow diluted the air with consequent deleterious effects. Avicenna (*ca.* A.D. 1000), anticipating Larrey by over 800 years, went so far as to consider this vapour a "brain poison." Christophe a Vega (1576) expressed the belief that serious symptoms, even death, could follow the inhalation of this gas. While the more superstitious were inclined to believe that death under these circumstances was the work of the devil, others were equally convinced that this was not true. This second group offered as evidence to the contrary the fact that Pope Clement VII met his death in this manner. He succumbed from breathing the fumes from burning torches carried before him in a religious parade. The first experimental evidence of this suffocating effect of fumes was offered by Boerhaave (1732), who demonstrated that an animal would quickly succumb to the vapour given off by burning organic matter.[4] An accidental experiment in human beings was described by Larrey (1814), the great military surgeon serving with Napoleon's armies. He noted in the case of a group of soldiers who slept in a closed chamber heated by a stove, that those who slept nearest the windows escaped, while those who slept nearest the stove succumbed. But most important of all was Larrey's conclusion, which agreed with that of his contemporaries Portal and Bichat. He concluded that "the brain and the nervous system which arises from it are almost suddenly paralyzed by the rapid transmission and diffusion of the deleterious carbonick principle, that is in the first place absorbed by the lungs and carried to the brain with the arterial blood. . . ."

Anoxia and the Development of Anaesthesia[5]

Coincident with this development of the idea that certain types of gases could replace the oxygen in the air with disturbing if not disastrous effects, some similar

[4]A review of the articles appearing on this subject in the eighteenth and the first part of the nineteenth centuries indicated that it was not only carbon monoxide that could supplant the oxygen in the air to produce asphyxia. The surcharging of inspired air with carbon dioxide resulting from fermentation, or even the presence of gases from decaying organic matter was also able to do this.

[5]A more complete history of cerebral anoxia with its relation to anaesthesia can be found in the writer's monograph on this subject (2).

qualities of the gas now known as nitrous oxide were observed by Priestly (1774). Because of hilarious behaviour of individuals inhaling this vapour, it was called "laughing gas." This property was therefore utilized to produce a narcotic effect similar to alcohol. It was soon suspected that the convulsive seizures sometimes associated with its use were due to the accompanying anoxaemia and were not apt to occur if a sufficient amount of oxygen was used along with it. Even though it was observed that injuries occurring while under the influence of nitrous oxide were not attended by pain, the idea of its being used as an anaesthetic agent was not quickly appreciated. It was Sir Humphrey Davy who, while experimenting on himself with this gas, found that the pain of an erupting wisdom tooth was considerably alleviated. He therefore recommended it (1800) in surgical procedures as a means of destroying pain. The peculiar effects of nitrous oxide, now recognized to be anoxic in origin, would require another century and more to be fully evaluated.

With the continued use of nitrous oxide as an anaesthetic, certain features of its nature became increasingly apparent. It seemed certain that there existed a degree of inherent narcotic action of this gas as compared with an inert gas such as nitrogen. On the other hand, a considerable degree of anoxaemia was also present in deep surgical anaesthesia. Moreover, this anoxaemia seemed to reinforce the anaesthetic action of the gas. This was shown in the untoward effects of nitrous oxide as manifested by the complicating symptoms which were strongly reminiscent of anoxia. This curious admixture of the narcotic and anoxic effects of nitrous oxide left its status confused.[6] This was especially true with respect to the symptomatology which preceded death in fatal cases. Here matters stood until the early 1930's.

Cerebral Anoxia and Nitrous Oxide

It was at this point that the writer entered the picture purely by chance. He was then in charge of the Neuropathology Laboratory of a large general hospital. As a result of serious complications of nitrous oxide anaesthesia, nine patients died within a short interval of time, while another survived with severe crippling residuals. A careful study of the brain in the fatal cases disclosed a fairly typical pattern of progressive changes in the cerebral gray matter in the form of patchy and laminar necrosis. This alteration was most marked in the motor and visual cortex, less so in the parietal and frontal areas. Necrotic changes in the globus pallidus, so characteristic of fatal cases of carbon monoxide "poisoning," were also present. These alterations first became evident in the brain of a patient who survived for 37 hours. They became progressively more marked as the survival

[6]In what is probably the first comprehensive treatise on the physiology of anaesthesia, Claude Bernard (3) raised the question whether anaesthesia was after all simply a form of asphyxia because both produced unconsciousness. Thus the physiological state of narcosis which is now referred to as anaesthesia, and "asphyxia" as its most serious complication were simultaneously evaluated. We cannot now tell how Bernard would have dealt with the complex problems relating to the chemistry and physiology of nitrous oxide which presented themselves in the next half-century. But his answer, and the reason therefore, were quite simple. No, anaesthesia was not asphyxia, for in anaesthesia the arterial blood retained its normal colour and oxygen content.

period stretched into days and weeks. These periods were so varied as to permit the elaboration of a fairly complete chronological picture of the entire process. When the results of this study were submitted by the writer to Dr. Yandell Henderson for his opinion, he promptly recognized that brain damage in these cases was unquestionably due to the occurrence of anoxaemia.

There has been much discussion as to the precise role of anoxaemia in the administration of nitrous oxide anaesthesia. Some astute anaesthetists on both sides of the Atlantic insisted that it was not the nitrous oxide gas that was at fault, but rather the way in which it was administered. The present writer, who makes no pretence of having any technical experience in anaesthesia, could only reply, "Whereas these unfortunate individuals were once alive, they are now dead. They experienced clinically what seemed to be an anoxaemic episode under nitrous oxide anaesthesia, and after death, their brains are stamped with unequivocal signs of an anoxic process." It was up to the academicians in the newly developing specialty of anaesthesia to debate the question of the precise mechanism of the obvious cerebral anoxia.[7]

The different viewpoints of the "schoolmen" on the subject of nitrous oxide were variously expressed. Some were a little piqued that a rank "outsider" would dare to speak thus against their favourite anaesthetic agent. Others welcomed the study as a disclosure of the real dangers in its use. At any rate, several very practical results followed this pronouncement. Soon a purer type of nitrous oxide was produced by the manufacturers, more accurate machines were developed to administer it, and improved methods with the use of larger percentages of oxygen were forthcoming. Viewed from this angle, the disclosure of the dangers of nitrous oxide was well worthwhile. At least, it served as a warning to the novices who had used the gas without due attention to the risks involved.

The studies of individuals other than the author, dealing with the untoward effect of nitrous oxide (5, 6, 7) established beyond question the fact that this agent was capable of producing profound, irreversible, and at times lethal effects of anoxia if not carefully used. In many instances, the warning signs of defective oxygenation of the brain (hypoxia) were quickly recognized and the tide turned in the direction of recovery. Experience with this agent in the past two decades and more has proven that, when properly handled, nitrous oxide could still serve as a useful agent although in the writer's experience, accidents still occurred. These accidents seem to complicate nitrous oxide anaesthesia more often when combined with large doses of pre-anaesthetic drugs and/or other anaesthetic agents.

Hypoxia and anoxia were not alone the results of nitrous oxide anaesthesia. In the same period in which this agent was being investigated, a number of cases

[7]And this is precisely what happened. The publication of a monograph on this subject (4) some three years after publication of the first somewhat extended report was followed by an exacerbation of a latent argument among the anaesthetists of England. These divided themselves into protagonists and antagonists on the subject of nitrous oxide anaesthesia, using the pages of the famous *Lancet* of London as their sounding board. The monograph was used with some apparent success by the "antis" against the "pros," but with the author always in the crossfire of the feud.

with fatal outcome from other inhalation anaesthetic agents came to light. Cyclopropane, for example, was found to produce fatal effects of oxygen-want (8). The point to be made in this connection is that most general anaesthetic agents can produce brain damage by this means.[8] This brings to mind the statement of Beecher and Todd (10) to the effect that hypoxia-anoxia is still the greatest enemy of the anaesthetist.

Contributions of Anaesthesia to the Current Concept of Hypoxia-Anoxia

This brief review of interest in anoxia over the past quarter-century makes it clear that one of the most important aspects of this subject lies in its connection with anaesthesia. Moreover, since this renewed interest in cerebral anoxia came about through the effects of one of the popular anaesthetic agents, that is, nitrous oxide, it is worthwhile to note the contributions to this subject that have been made in the past quarter-century. At this point, the present writer is obliged to speak largely from his own experience, drawing conclusions from both his clinical and his pathological observations. It is recognized, of course, that drawing lessons from pathology is none too popular today. Animal experimentation seems rather to be the method of choice. Were it not for the fact that animals do not always react like human beings from the viewpoint of objective behaviour, and that their brains do not present the same residuals from experimentally induced anoxia, observations on the human "animal" would likely be discarded entirely. Nevertheless, some lessons have been learned which seem to be of primary interest to those who carry on their minds and hearts the responsibility for the well-being of their patients.

It is well to point out these specific lessons and then to deal with them one by one.

(1) All anaesthetic agents are body poisons, always inherently dangerous and sometimes lethal, if not properly used.

(2) These agents act on the body tissues chiefly through their narcotic actions in so far as their normal behaviour is concerned. Because the grey matter of the brain (that is, the portion which contains the nerve cells) is most vulnerable to the effects of oxygen-want as well as narcosis, it is in this portion of the nervous system that structural changes are first to appear.

(3) The narcotic effect of anaesthetic agents seems to be a double one, the

[8]It is well known, of course, that the primary noxious effect of chloroform is on the liver; no cases known to the present writer bear out the idea that cerebral hypoxia occurs under its influence. As for ethyl ether, the problem is not entirely clear (9). In the very few cases studied by the writer, evidence seems to imply that there is a noxious effect on the cerebral gray matter, but the *pattern of change* is not typical of anoxia. The cerebral gray matter, especially the cortex, appears to become brittle and to undergo a peculiar fissuring and fragmentation, and in some instances at least, this change is particularly marked about the blood vessels. The writer has chosen to leave the matter of the noxious effects of ether on the brain as an unsolved problem for the present.

primary effect as such acting directly on the cortical nerve cells, while another secondary effect serves to depress the vital centres, particularly the vasomotor centre.

(4) While the desired narcotic effect of an anaesthetic agent is its tendency to depress the nerve cells of the cerebral cortex, an associated anoxic effect is achieved through an impairment of the vital centres, disturbing respiration and circulation. Alteration in vasomotor functions tends to result in ischaemia, with localized alterations in the brain tissues.

(5) Clinical evidence seems to indicate that an accumulative effect on the respiratory, cardiac, and vasomotor centres is exerted by multiple pre-anaesthetic sedatives and anaesthetic agents used in conjunction therewith. Each drug acting in its own specific way, not infrequently tends to depress these centres unduly and to lead to their functional failure.

(6) The precipitation of an acute failure of the vital centres in the course of an anaesthesia is usually due to the combined effect of the anaesthetic agent or agents and any pre-existent factors which *per se* predispose to hypoxia.

(7) The best prevention of anaesthetic hypoxia-anoxia must lie in the personal qualifications of the anaesthetist—such as a knowledge of pre-anaesthetic status of the patient regarding his inherent potentials favouring the development of the anoxic state, his experience with the behaviour of the proposed anaesthetic agent, and constant attention to the status of the patient under the anaesthetic.

A brief elaboration of these individual observations will make clear certain fundamental aspects of the hypoxic-anoxic state as held currently by the present writer.

Anaesthetics as Brain Poisons

When anaesthetists in Great Britain were laying the foundations of their professional organization, Dr. Lucas suggested that the society adopt as its crest that of the Borgias, who were so expert in the matter of administering poisons. If the writer is not misinformed, this step was actually decided upon. The prime purpose of this crest was to keep the membership constantly reminded that the agents which they used were indeed poisons, but ones which could be skilfully adapted to the well-being of their patients. That these toxic substances could not only produce transitory ill-effects, but could also destroy the patient through excessive dosage or misapplication of technique should be thought of whenever an anaesthetic agent is being chosen.

Narcotic versus *Hypoxic Effects*

The desired anaesthetic effect is achieved through the narcotic action of the drug on the nerve cells of the brain. The cells in the sensory system (the thalamus and the sensory cortex) and the centre of consciousness in the upper brain stem constitute the specific targets for this effect. If this narcotic action is not *per se* a form of anoxia (that is, histiotoxic anoxia, acting through an interference with cellular oxidation), it closely resembles this process in its ultimate effects. But, while this desired effect is being accomplished, a coincident but less conspicuous

depressive effect on the vital centres is also taking place. If this effect becomes excessive, an untoward reaction of one or more of three centres may occur. There may be respiratory irregularities (respiratory centre), an impairment of the peripheral circulation with drop in blood pressure (vasomotor centre) may follow, or actual cardiac failure (cardiac centre) may occur. Such an episode is usually as unexpected as it is critical. The seriousness of this situation lies in the fact that it is precisely under such circumstances that cerebral hypoxia may be precipitated and under which, if not successfully dealt with, cerebral anoxia results with irreparable damage. The extent of this damage decides whether the patient will survive with certain degrees of intellectual deficit, or with the more disturbing widespread motor paralysis, or whether he will die either at once or after a variable interval.

The Dr. Jekyll and Mr. Hyde Effects of Anaesthesia

The boon of successful anaesthesia to the surgeon as well as to the surgical patient are beyond computation. But while the blessing of anaesthesia through narcosis of the cerebral nerve cells is being attained, a similar but much less evident depressive effect on the vital centres is also going on. Unfortunately, these effects may not be apparent until sudden failure of these centres takes place. A successful anaesthetic, therefore, is one in which perfect narcosis of the patient is achieved without any appreciable effect on the patient's vital functions. The possible failure of these functions through excessive depression and the resultant effects on the brain is indeed the "spectre which haunts every surgical amphitheatre." For this reason, it is impossible for the anaesthetist to pay too much attention to these functions, for any warning of disaster can come only by their abnormal responses.

The Specific Evil of Vasomotor Dysfunction

Only through long attention to the mechanism of brain damage has the present writer come to appreciate the great importance of vasomotor instability in the ultimate structural changes in cerebral anoxia. It is now known that cerebral damage incident to anoxia is not a diffuse affair, one which tends to affect the entire brain, rather one has to do with selective damage, for the nerve cells of certain cortical laminae are more vulnerable than others. Moreover, certain portions of the convolutions are first to undergo physical change. Finally, some areas of the cortex are more prone to suffer early and more profoundly. All these variations can best be explained by the intervention of some vascular factor. This conclusion also seems justified because areas of softening of the cerebral cortex and subcortex as well as specific patterns of architectural change occur which are undoubtedly the result of ischaemia. This is implied because only an occlusion or spasm of the local branches of the cortical arteries or arterioles can explain these results. It is, therefore, impossible to evaluate the total picture, either clinically or pathologically, without taking into consideration this secondary ischaemic change. Vasomotor instability *per se* not only produces cortical changes, but also prolongs and intensifies the alterations produced by anoxaemia incident to an impairment or failure of circulation. The only appropriate treatment that

remains available to the anaesthetist facing a serious hypoxic state is an attempt to restore vasomotor stability.[9]

Danger in the Multiplicity of Narcotic or Anaesthetic Agents

The writer's clinical contacts with patients who have suffered from the serious effects of a post-anaesthetic anoxic state has suggested the frequency with which several pre-anaesthetic drugs have been used to achieve preliminary sedation, and the multiplicity of anaesthetic agents that have been utilized in producing the subsequent anaesthesia. This has occurred so often, in fact, as to constitute in his mind one of the essential causes of an anaesthetic hypoxic episode. One visualizes the concept that the vital centres are individually influenced in different ways by the pharmacological action of each drug or agent. The introduction of each additional agent seems to add to the sum total of depression of the responsible nerve cells. Finally, the margin of safety is so much reduced that normal regulation is no longer possible. Under this state, any further insult to these centres results in their cessation of function with consequent cardiorespiratory collapse. Every young anaesthetist should become conscious of this problem to the end that any complexity of additional drugs or agents should be administered with great caution.

Importance of Pre-existent Factors Favouring Hypoxia-Anoxia

In a recent review of the verified cases of fatal post-anaesthetic anoxias (12), the predisposing factors which seemed to favour the precipitation of a hypoxic-anoxic disorder in the course of an anaesthetic were sought. This review suggested that so often in cases with serious or fatal results of anaesthetic anoxic states, evidence exists which suggests the presence of significant pre-existing factors. Among these factors are (i) racial and group predisposition, (ii) familial predisposition, (iii) pre-existing functional or organic nervous disorders, (iv) pre-existing pulmonary or cardiac disease, (v) excessive or prolonged sedation, (vi) acute or chronic alcoholism or narcotic addiction, and (vii) preoperative or operative haemorrhage. These factors need no special consideration, for their possible role in the production of an acute anaesthetic hypoxic state is all too evident. The point which needs to be emphasized is that these possibilities should always be reviewed with the patient before any induction of anaesthesia. In the writer's series of cases, many of the patients might well have been alive today had this precaution been followed.

The Anaesthetic Technician versus *Medical Scientist*

An outsider can only admire the rapidity with which this specialty of anaesthesiology has come to the fore in the past quarter-century. Among the most important of its achievements has been the recognition of the need of adequate training and supervised experience in the use of the various anaesthetic agents

[9]This can be accomplished in some instances by the use of procaine hydrochloride, 1 gm. to a litre of 5 per cent glucose, given intravenously two or three times a day, as long as there is any hope of restoring the patient to consciousness or as long as cerebral dysrhythmia (as determined by an electroencephalogram) persists (11).

and the complex equipment with which they are administered. At the present time, there is little to be desired in this regard in so far as the larger hospitals and medical centres are concerned. But there remains still a large area in which anaesthesia is administered by poorly trained personnel. In these areas, anaesthetic accidents still occur. To assume a pharisaical attitude that all is well with anaesthesia, that any reference to anaesthetic anoxia is now quite out of date, is not only foolish but neglectful to the point of being criminal. What is to be done about the general practitioner in a small community who steps in and gives an occasional anaesthetic for the local surgeon? Should there be an effort to make him aware of the technical intricacies of his problem and the nature of the "brain poisons" which he administers? It is true that time will solve this difficulty, when all anaesthetists are well trained, but what of the fatal cases that will occur in the meantime? Whether this situation calls for an interval programme of instruction for these "temporary anaesthetists" or whether such practitioners of the art should be limited to the use of the simpler agents with which they may become more easily acquainted, is a problem for groups such as yours. The lesson which our present concepts of anoxia teaches is that this complication usually comes from lack of knowledge of the agent and techniques of its use. Disabilities from anaesthetic accidents can be so permanent or even fatal that some efforts should be made to avert the tragedies which follow their occurrence. But the responsibility of your speaker, a "layman" in so far as anaesthesia is concerned, can be only to emphasize the dangers of cerebral anoxia and some of the ways in which it may be avoided.

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THE MANAGEMENT OF ACUTE HYPOXIA[1]

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ACUTE HYPOXIA may develop in a large variety of medical and surgical conditions. It may range from relatively mild or short-lasting episodes to the ultimate in severity as exemplified by ventricular fibrillation and cardiac standstill. The subject of acute hypoxia has been dealt with extensively in the literature, but the main emphasis usually has been laid on cardiac arrest. Yet, any condition or event, affecting *either* respiration *or* circulation *or* both, which acutely leads to suboxygenation of tissues constitutes acute hypoxia.

While it can be readily appreciated that the diverse causes of acute hypoxia and their combination are legion, it is equally clear that, either because of the mild degree or because of extremely short duration, obvious clinical signs and sequelae may be entirely absent or at least they cannot be detected with the diagnostic means at our disposal. Hence, from a practical point of view, such hypoxic events are of little significance.

On the other hand, cardiac arrest is by no means the only acute hypoxic episode in which sequelae of hypoxia are present and need vigorous treatment. All too often treatment for one of the less dramatic hypoxic events is not instituted and the fact is accepted that the patient will regain consciousness less promptly than might be expected otherwise, that he will be confused, nauseated, or restless. This applies equally to anaesthesia, diverse states of unconsciousness, and hypoxia not associated with coma. It behoves us then in all cases of acute hypoxia to weigh the severity and duration of the event and decide whether for a particular patient under the particular circumstances prevailing the hypoxia was severe enough in degree and duration to merit active treatment.

An attempt will be made to describe the management of severe hypoxia.

TREATMENT

(*a*) It is a general principle that whenever an untoward reaction occurs from whatever cause, the first step must be to correct that cause if it is known. This same principle applies to the management of acute hypoxia. If at all possible the aetiological factor responsible for the hypoxia must be identified and corrected and a determined effort must be made to provide adequate tissue oxygenation.

(*b*) Because of its great intolerance to deprivation of oxygen, the central nervous sytem, and in particular the brain, present the most formidable obstacle to satisfactory recovery from acute hypoxia. The crudeness of our tests prevents us from ascertaining minor degrees of cerebral impairment while in extreme cases

[1]From the Department of Anaesthesia, University of Saskatchewan and University Hospital, Saskatoon, Sask. Presented at the Meeting of the Western Divisions, Canadian Anaesthetists' Society at Victoria, B.C., April 28–30, 1960.

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the clinical picture is one of coma, convulsions, periodic breathing or complete apnoea. Between these two extremes all grades of intermediate stages exist.

It must be accepted as axiomatic that "nervous tissue once destroyed does not regenerate and cannot resume function." Hence, depending upon the duration and severity of the hypoxic episode, there will be a degree of morphological damage which is irreparable. This in itself may be sufficient to cause death or irreversible coma, leading ultimately to a fatal outcome.

Just as oedema will occur anywhere in the body where hypoxia has interfered with tissue integrity, so also will cerebral oedema supervene if the brain has been exposed to abnormally low oxygen tensions. Indeed the brain is more likely to be affected by oedema since it reacts in this fashion to a slightest insult. While in many parts of the body, with the exception of the lungs, the oedematous reaction is of little immediate consequence, it is of grave significance when it affects the brain. This is largely due to the fact that the organ is enclosed in a bony casing and once displacement of cerebral spinal fluid has allowed for maximum expansion the organ then becomes compressed upon itself. This places the brain into triple jeopardy. First, the blood supply is impeded through external compression of the cerebral vascular bed; second, nerve cells are mechanically compressed; and third, gas exchange between capillaries and cells is impeded through the interposition of oedema fluid.

It is reasonable to assume that, while some cells or groups of cells have been damaged beyond repair and others are entirely unaffected, there will be some nervous elements which have not been sufficiently injured by hypoxia to cause their immediate death and under proper management may be able to recover. However, the recurrence of a restricted oxygen supply may be sufficient to inflict a final insult upon these elements, converting reversible into irreversible damage. In this way a vicious cycle of hypoxia, oedema, more hypoxia is initiated and this will continue, unless treated, despite the fact that the original hypoxic episode may have been brought under complete control. Thus originally limited damage may assume fatal proportions at a time when it would appear that the crisis has passed.

In 1953, Sadove *et al.* (1) described their concept of a "dehydration therapy" which had been worked out by that group. They had found that the administration of hypertonic 50 per cent dextrose solution did in fact accelerate the waking-up process of patients who had been in cardiac arrest. However, they found that this state was not a permanent one, and that "rebound oedema" usually caused some regression in the state of consciousness following initial improvement. They were able by repeated administrations to maintain consciousness and obtain a high percentage of recoveries.

The basic concept of reducing cerebral oedema by the administration of hypertonic solutions is not new. Following the work of Weed and McKibben (2) as early as 1919, many attempts have been made to reduce intracranial pressure by use of hypertonic solutions. Among the agents tested at one time or another were sodium chloride, sodium sulphate, sodium bicarbonate, magnesium sulphate, sucrose, dextrose, and others. While sodium chloride and 50 per cent dextrose are followed by the so-called "rebound oedema," 50 per cent sucrose which does

not show rebound oedema to the same degree is more damaging to renal function. In later years, quadruple concentrated plasma, plasma volume expanders, in particular high molecular-weight dextran, and serum albumin were added to the list of substances capable of influencing brain oedema. With all these agents adequate kidney function was maintained by the administration of diuretics while recurrence of the oedema was further prevented by rigid control of fluid and electrolyte administration, the correct balance of which in turn depended upon adequate and well-controlled renal function.

The introduction of *urea* in a clinically useful solution for parenteral administration has revolutionized the treatment of cerebral oedema. It had been found in 1927 that urea was effective in reducing cerebral spinal fluid pressure in animals (3, 4), but it was not until 1956 that Javid and Settlage (5) first reported on its effect on cerebral spinal fluid pressure in man. However, one disadvantage of the parenteral administration of urea was the occasional occurrence of haemoglobinuria. Only recently has this difficulty been overcome by the preparation of lyophilized urea dissolved in invert sugar. This agent has the added advantage of being a diuretic in its own right. Anyone who has observed the effect of this therapy in neurosurgical procedures must be impressed by its performance.

(*c*) A further valuable adjunct to the management of the sequelae of acute hypoxia is *hypothermia*. There are three basic reasons for its efficacy. One is the reduction of the tissue oxygen demand and thus the provision of further protection of partially damaged brain cells; secondly, hypothermia assists in the control of cerebral oedema and, lastly, it controls the hyperpyrexia so often associated with severe brain damage. Cooling may be done by any of the accepted methods and a temperature of between 30 and 32° C. is aimed at. It is, of course, important that shivering be controlled and that both the body temperature and the electrocardiogram be continuously monitored. Oesophageal temperature readings are preferable to rectal temperatures.

If prolonged maintenance of hypothermia is needed an attempt might be made to maintain the lowered temperature by the use of fans or, if available, in a cold-room. There are some definite nursing difficulties, especially with regard to skin care, when the patient is maintained in hypothermia blankets for any length of time.

(*d*) As in all cases of coma, meticulous attention must be paid to the airway and to adequate tidal exchange. Repeated tracheobronchial toilet is mandatory and, if necessary, artificial respiration is carried out by means of a mechanical ventilator or inadequate spontaneous respiration is assisted using an assistor. If coma is prolonged beyond 24 hours, tracheostomy should be considered.

(*e*) Vital signs are continuously monitored and treatment for cardiovascular embarrassment is symptomatic. Digitalization may be required, the electrolyte balance must be maintained in the presence of a regime of dehydration and an adequate caloric intake must be assured. An indwelling catheter serves as a means of observing and recording urinary output. Antibiotics are administered prophylactically. If the coma is prolonged beyond a few days tube feeding may have to be instituted.

(*f*) If hypoxia has not resulted in coma but only in post-hypoxic restlessness

as is seen not infrequently in the immediate postoperative period, this must not be interpreted as a manifestation of pain. Hence, narcotics are not indicated in the majority of cases. In these instances it is well to administer high concentrations of oxygen, check tidal and minute volumes, and remember the possibility of diffusion hypoxia. Assistors may again be indicated.

Prognosis

In all cases of very severe and prolonged hypoxia the prognosis should be guarded. Following cardiac arrest, in particular, it is most unrewarding to prognosticate. However, three groups of observations can be of assistance in this regard.

(*a*) *Electroencephalogram.* If following severe hypoxia no electroencephalographic activity is discernible, the prognosis is grave indeed. On the other hand the presence of electroencephalographic activity does not assure recovery.

(*b*) *Respiration.* If following a severe hypoxic episode respiration ceases and does not resume within half an hour or thereabouts, the outlook is again grave. Patients whose respiration has never ceased have a much better prognosis.

(*c*) *Cardiovascular function.* The outlook is grave if cardiovascular function cannot be maintained and if prolonged intractable hypotension ensues.

However, it is important to emphasize once again that these signs are guides only and are not of absolute prognostic value.

Summary

The management of acute hypoxia in its more severe forms is based primarily upon the control of cerebral oedema. With the advent of a clinically useful form of urea, all agents previously employed for this purpose have become obsolete. The control of cerebral oedema shortens coma and increases survival. Hypothermia is a further valuable adjunct which supplements the action of urea, reduces oxygen demand by injured tissues, and controls hyperpyrexia. In all other regards the management of the patient, unconscious from hypoxia, is identical to that which applies generally to the care of the unconscious patient. If hypoxia has not resulted in coma, care must be taken to interpret correctly post-hypoxic restlessness, and depressant drugs must be avoided.

The prognosis should always be guarded. The electroencephalogram is a valuable aid in assessing the extent of cerebral impairment. Early resumpton of spontaneous respiration and stability of cardiovascular function in the post-hypoxic period are favourable signs, but are not of absolute prognostic value.

Résumé

L'hypoxie aiguë peut survenir dans une grande variété de cas de médecine ou de chirurgie et cela ne se limite pas aux cas où il s'est produit un arrêt complet de la circulation.

Le traitement efficace de l'hypoxie aiguë tient, pour une grande part, au

contrôle de l'œdème cérébral. Ce contrôle est devenu plus facile grâce à l'apparition de l'urée qui, en mème temps, a apporté plus de sécurité et permet de prévoir les résultats. L'œdème cérébral, après que la crise aiguë d'hypoxie a été vaincue, cause des dommages cérébraux additionnels et, ainsi, il peut rendre irréversibles des lésions qui étaient réversibles.

Un autre précieux adjuvant dans le traitement de l'hypoxie aiguë est l'hypothermie. Non seulement l'hypothermie aide à contrôler l'œdème cérébral mais elle réduit en plus la demande d'oxygène de la part du cerveau et elle prévient l'hyperpyrexie.

Les malades qui demeurent comateux doivent être traités par ailleurs de la même manière que le sont tous les malades inconscients. En d'autres termes, il faut leur assurer une fonction respiratoire adéquate, supporter leur système cardiovasculaire et, si nécessaire, contrôler leur équilibre hydrique et électrolytique; il faut alimenter ces malades soit par tubes, soit par voie parentérale.

Il peut arriver qu'un malade ne soit pas comateux à la suite d'une hypoxie aiguë, mais qu'il demeure agité. Cette situation commande une oxygénation adéquate et, peut-être, une respiration assistée plutôt que des narcotiques et des sédatifs qui seraient susceptibles d'accroître l'agitation et de déprimer la respiration.

L'électroencéphalogramme, en ces circonstances, peut devenir précieux pour établir un pronostic. Si l'apnée persiste ou si l'hypotension n'est pas corrigible, le pronostic est mauvais. Toutefois, aucun de ces signes ne peut prendre une valeur absolute de pronostic et ils ne peuvent servir que comme indices de l'issue probable.

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A STUDY OF CHLOROFORM ANAESTHESIA IN A PRECISION SYSTEM:

II. THE EFFECT ON CIRCULATORY DYNAMICS AND ANAESTHETIC MORBIDITY[1]

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SINCE THE GENERAL ACCEPTANCE of halothane, several authors have speculated about the possibility of reintroducing chloroform as a clinical agent, because the chemical and physical properties of these two are akin. It was felt that any new clinical studies of chloroform must be done with the same care and attention to detail as have been found necessary with halothane since the physiological and pathological effects on vital organs appear to be similar. This report deals with the effect of chloroform on circulatory dynamics and post-anaesthetic morbidity when it was used clinically in a precision system.

MATERIALS AND METHODS

Data were collected from 154 patients who underwent major operations. Anaesthetic management was the same as described in the previous report (1).

Circulatory dynamics were observed closely in each operation. Pulse rate and arterial blood pressure were recorded at 5 min. intervals by palpation and auscultation respectively (2). The electrocardiogram (lead 2) was monitored in those patients with evidence of heart disease. The mean blood pressures and pulse rates during maintenance were obtained by averaging the individual readings, starting 10 min. after induction of anaesthesia, and ending when chloroform administration was discontinued at the end of the operation. The recordings noted during the 10 min. period immediately following induction of anaesthesia were tabulated separately, as were the pre-induction recordings, and those at the end of the operation. Stroke volume and cardiac output were estimated from recordings of the vital signs (3).

Post-anaesthetic morbidity and mortality were recorded and reviewed in each case.

RESULTS

Circulatory Dynamics

Analyses of the variation in blood pressure, pulse rate, estimated stroke volume, and cardiac output are shown in Table I. Figure 1 shows the mean variation and standard deviation for two groups of patients who underwent

[1]Read at the Second World Congress of Anesthesiologists, Sept. 4–10, 1960, Toronto, Ont.
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TABLE I

CIRCULATORY DYNAMICS DURING CHLOROFORM-NITROUS OXIDE ANAESTHESIA IN A NON-REBREATHING SYSTEM AND ARTIFICIAL RESPIRATION
A. GASTRECTOMY AND INTRATHORACIC OPERATIONS IN SUPINE HORIZONTAL AND LATERAL FLEXED POSITION (41 PATIENTS)

							Before anaesthesia					Induction					Maintenance					End of anaesthesia				
	Age	Sex	Build	Physical state	Anaesthesia time	Muscle relaxant	Systolic BP	Diastolic BP	Pulse rate	Stroke volume	Cardiac output	Systolic BP	Diastolic BP	Pulse rate	Stroke volume	Cardiac output	Systolic BP	Diastolic BP	Pulse rate	Stroke volume	Cardiac output	Systolic BP	Diastolic BP	Pulse rate	Stroke volume	Cardiac output
					(min.)		(mm. Hg)		(min.)	(ml.)	(L.)	(mm. Hg)		(min.)	(ml.)	(L.)	(mm. Hg)		(min.)	(ml.)	(L.)	(mm. Hg)		(min.)	(ml.)	(L.)
	30	M	M	2	85	G	124	72	120	66	7.9	126	72	122	69	8.2	120	78	140	57	8.0	126	86	140	52	7.2
	35	M	O	3	150	dMC	104	76	100	50	5.0	124	82	104	52	5.4	112	82	102	47	4.7	112	82	106	47	4.9
	37	M	M	1	150	G	108	60	62	67	4.1	110	68	86	60	5.1	122	80	98	53	5.2	140	88	80	53	4.2
	37	F	M	1	145	G	114	70	80	60	4.8	124	74	90	60	5.4	120	80	108	51	5.5	122	80	90	52	4.7
	39	M	O	2	280	G	110	74	60	52	3.1	112	76	74	50	3.7	132	96	116	38	4.0	128	92	120	41	4.9
	41	F	L	2	125	dMC	90	70	100	45	4.5	110	76	104	48	5.0	116	80	82	47	3.8	130	86	80	47	3.8
	41	M	O	2	240	G	100	70	70	50	3.5	100	70	84	50	4.2	90	70	86	45	3.9	100	74	80	46	3.7
	44	M	L	2	215	dMC	106	70	80	51	4.1	106	74	80	47	3.7	146	100	80	39	3.2	160	100	86	45	4.0
	45	M	O	2	145	G	120	80	100	47	4.7	120	80	100	47	4.7	116	84	120	40	4.8	120	90	110	35	3.9
	45	M	M	1	145	G	120	76	90	51	4.7	124	80	92	47	4.3	126	90	102	40	4.2	128	90	110	40	4.4
	45	M	O	2	180	G	138	100	80	35	2.8	140	100	100	35	3.5	144	110	130	26	3.3	152	108	132	32	4.2
	45	M	M	3	125	dMC	106	70	90	51	4.6	106	76	102	44	4.5	90	60	96	53	5.1	96	70	90	46	4.1
	48	F	L	3	135	G	110	64	90	52	5.1	106	64	92	55	5.0	120	80	92	45	4.0	116	78	80	53	4.2
	49	F	O	2	150	dMC	90	60	70	51	3.6	90	60	80	51	4.7	102	66	64	51	3.2	120	80	84	45	3.8
	49	M	O	3	120	dMC	116	90	70	31	2.1	130	100	94	27	1.8	134	94	64	36	2.2	150	100	68	37	2.5
	54	M	O	2	155	G	140	90	82	40	3.2	132	88	98	38	3.7	152	102	90	34	3.0	162	110	80	30	2.3
	54	M	O	2	290	dMC	160	104	106	35	3.7	156	100	110	37	4.1	150	100	130	35	4.5	140	90	150	40	6.1
	55	M	O	2	250	G	114	65	90	50	4.5	106	65	90	49	4.4	94	66	110	43	4.7	106	70	100	44	4.4
	55	M	M	3	135	G	200	120	100	37	3.7	200	120	100	37	3.7	190	120	108	32	3.5	220	140	100	28	2.8
	56	F	L	2	230	dMC	130	80	110	45	4.9	140	90	120	39	4.7	150	106	92	25	2.0	150	100	100	32	3.2
	57	F	M	3	255	G	136	90	80	37	3.0	130	90	84	34	2.7	118	82	102	36	3.7	120	84	100	35	3.5
	58	F	O	2	180	G	120	90	80	21	2.1	110	76	92	38	3.5	124	80	100	41	4.1	130	76	100	48	4.8
	58	M	L	3	80	G	110	80	88	32	2.8	118	86	106	31	3.2	130	92	116	30	3.4	132	90	120	34	4.0
	58	M	M	1	190	G	120	80	70	38	2.7	130	90	90	32	2.8	130	84	90	40	3.7	140	92	100	35	3.5
	58	F	M	3	165	dMC	160	94	96	43	4.1	200	110	84	46	3.9	250	120	80	60	4.8	250	120	90	59	5.5
	59	M	L	2	75	G	112	64	80	51	4.1	118	74	94	44	4.1	130	93	108	29	3.1	130	94	102	28	2.7
	59	M	O	2	150	G	130	80	100	43	4.3	124	80	94	40	3.7	128	88	108	32	3.5	130	90	100	32	3.1
	59	M	O	2	185	G	130	80	82	43	3.5	126	88	90	32	2.9	120	86	98	31	3.0	132	90	100	33	3.3
	60	M	M	2	310	G	130	70	90	53	4.8	114	74	96	41	3.4	100	74	120	35	4.2	96	70	124	36	4.4
	61	M	L	3	290	G	104	60	80	37	3.0	96	64	96	42	4.1	104	78	100	31	3.1	102	78	100	30	2.9
	61	M	M	1	140	G	106	80	70	29	2.0	100	70	90	38	3.5	140	100	80	27	2.0	150	92	80	37	3.5
	63	M	M	1	140	G	130	90	70	29	2.0	122	80	82	36	2.9	138	92	84	36	3.0	140	88	90	37	3.3
	64	M	M	3	180	dMC	100	60	64	47	3.0	138	84	72	42	3.0	154	96	80	33	2.6	140	92	82	32	2.5
	67	M	L	1	190	dMC	140	80	82	43	3.5	140	80	90	44	4.0	116	74	76	38	3.0	110	66	80	44	3.5
	68	F	M	2	75	G	150	90	80	36	2.8	135	88	82	31	2.5	140	92	98	29	2.8	148	100	88	24	2.0
	70	M	O	3	135	G	180	90	100	50	5.0	140	82	108	41	4.2	144	90	112	32	3.6	150	100	110	24	2.5
	71	M	L	2	125	G	140	80	100	41	4.1	126	74	82	40	3.2	130	92	118	22	2.5	140	86	120	35	4.1
	73	F	O	3	270	G	140	70	80	51	4.1	130	70	110	46	5.1	120	76	110	34	3.8	110	70	120	36	4.2
	75	M	L	3	175	dMC	70	60	80	35	2.8	100	70	90	29	2.6	122	72	70	38	2.6	140	90	74	27	1.3
	75	M	M	2	155	G	140	60	90	61	5.5	130	60	100	55	5.5	176	96	116	38	4.4	174	100	120	34	4.1
	79	F	L	3	120	dMC	180	90	160	45	7.3	155	84	120	39	4.7	160	90	124	35	4.2	180	92	118	42	5.0
Mean	55				174		126	78	87	45	4.0	125	79	94	43	4.0	132	88	100	39	3.8	137	90	100	39	3.8
S.D.							25	14	20	10	1.3	23	13	12	9	1.1	29	14	18	9	1.1	30	14	19	9	1.1
S.E.							4	2	3	2	0.2	4	2	2	1	0.2	5	2	3	1	0.2	5	2	3	1	0.2

TABLE I (*continued*)

B. CHOLECYSTECTOMY AND RELATED OPERATIONS IN SUPINE HORIZONTAL POSITION (29 PATIENTS)

							Before anaesthesia					Induction					Maintenance					End of anaesthesia				
	Age	Sex	Build	Physical state	Anaesthesia time	Muscle relaxant	Systolic BP	Diastolic BP	Pulse rate	Stroke volume	Cardiac output	Systolic BP	Diastolic BP	Pulse rate	Stroke volume	Cardiac output	Systolic BP	Diastolic BP	Pulse rate	Stroke volume	Cardiac output	Systolic BP	Diastolic BP	Pulse rate	Stroke volume	Cardiac output
					(min.)		(mm. Hg)		(min.)	(ml.)	(L.)	(mm. Hg)		(min.)	(ml.)	(L.)	(mm. Hg)		(min.)	(ml.)	(L.)	(mm. Hg)		(min)	(ml.)	(L.)
	18	F	O	1	90	dMC	100	70	62	64	3.9	104	70	90	66	5.9	98	68	82	65	5.2	96	60	70	74	5.2
	23	F	M	2	75	dMC	118	80	70	59	4.1	104	72	72	61	4.2	96	54	80	76	6.1	102	64	82	69	5.6
	33	F	M	1	170	dMC	102	64	78	63	4.9	106	68	82	60	4.9	110	68	74	62	4.6	104	62	72	66	4.7
	34	M	M	1	130	dMC	120	78	90	55	5.0	120	80	90	53	5.2	124	94	90	41	3.7	110	90	100	37	3.7
	34	F	M	1	105	G	120	70	80	65	5.2	108	64	120	65	7.2	110	70	130	59	7.6	110	74	118	55	6.5
	35	F	O	2	110	G	110	60	70	69	4.8	108	60	96	69	6.6	122	84	120	50	6.0	130	90	108	46	4.9
	38	F	M	1	145	G	108	68	88	63	5.6	108	72	96	54	5.2	124	90	100	42	4.2	132	90	100	46	4.6
	40	F	M	1	90	dMC	100	70	60	50	3.0	96	62	72	57	4.1	104	70	68	53	3.6	120	78	70	52	3.7
	46	F	O	2	155	G	124	72	80	57	4.6	122	78	100	49	4.9	126	80	122	49	6.0	134	86	122	47	5.7
	51	M	O	2	155	dMC	140	78	84	55	4.6	116	72	96	50	4.8	130	90	94	36	3.3	134	90	82	41	3.1
	53	F	O	2	60	G	128	70	80	57	4.6	120	74	94	48	4.5	118	80	104	41	4.2	118	80	100	40	4.0
	54	F	M	1	115	G	110	66	90	52	4.7	104	62	84	53	4.4	98	66	110	46	5.1	108	68	100	49	4.9
	56	F	M	1	205	G	126	80	90	43	3.9	130	84	96	41	3.9	118	78	82	41	3.3	130	88	80	36	2.8
	56	F	O	2	110	G	136	80	80	48	3.9	128	80	90	44	4.0	126	80	92	43	4.0	140	88	90	41	3.7
	57	F	O	2	230	G	110	70	72	46	3.1	106	70	78	43	3.4	104	72	80	38	3.0	102	70	80	41	3.2
	57	M	O	3	150	G	120	60	72	62	4.4	124	74	74	48	3.5	130	80	126	45	5.6	130	76	120	49	5.9
	59	M	O	2	90	G	130	70	60	54	3.3	122	74	92	46	4.2	112	76	120	39	4.6	110	70	120	44	5.3
	60	M	M	1	120	G	122	74	68	45	3.0	120	78	84	40	3.3	126	90	128	29	3.7	136	90	110	34	3.8
	63	M	O	3	225	G	128	70	80	51	4.1	128	68	90	52	4.7	124	80	98	37	3.6	132	80	82	41	3.4
	63	F	O	2	215	G	130	70	72	51	3.7	124	72	86	46	4.0	126	86	94	32	2.9	136	90	80	33	2.6
	65	M	O	3	105	G	170	90	80	48	3.9	176	94	96	47	4.5	164	92	92	43	4.0	170	100	80	38	3.1
	68	F	M	2	100	G	102	80	70	24	1.6	104	76	72	29	2.0	104	68	80	37	3.0	102	66	80	39	3.1
	68	F	M	3	95	G	120	84	80	29	2.2	110	76	88	32	2.8	112	70	82	39	3.1	122	76	80	38	3.0
	71	M	L	3	170	G	118	68	70	43	3.0	110	60	70	48	3.4	102	72	108	30	3.1	110	74	112	32	3.6
	71	M	L	3	80	G	90	60	62	38	2.1	90	60	86	37	3.2	106	72	100	32	3.2	112	80	100	26	2.5
	72	F	M	2	105	G	140	80	100	40	4.0	138	78	98	42	4.1	124	76	106	36	3.8	140	80	100	41	4.1
	73	M	O	4	170	dMC	138	80	90	38	3.4	144	80	90	42	3.8	144	78	86	44	3.8	130	72	84	43	3.2
	78	M	O	3	125	G	160	90	100	36	3.6	146	88	102	30	3.0	150	94	100	26	2.6	160	100	90	25	2.1
	83	F	M	3	145	G	124	68	120	38	4.6	124	70	120	36	4.4	110	60	120	40	4.8	122	68	112	37	4.1
Mean	55				132		122	73	79	50	3.9	119	73	90	48	4.3	119	77	99	43	4.2	124	80	95	44	4.0
S.D.							17	8	13	11	.9	17	8	12	10	1.0	16	10	17	11	1.2	16	11	16	11	1.1
S.E.							3	2	3	2	.2	3	2	2	2	0.2	3	2	3	2	0.2	3	2	3	2	0.2

TABLE 1 (*continued*)

C. Lower Abdominal and Abdominal Perineal Operations in Trendelenberg and Head Low—Lithotomy Position (44 patients)

	Age	Sex	Build	Physical state	Anaesthesia time (min.	Muscle relaxant	Before anaesthesia: Systolic BP (mm. Hg)	Before anaesthesia: Diastolic BP (mm. Hg)	Before anaesthesia: Pulse rate (min.)	Before anaesthesia: Stroke volume (ml.)	Before anaesthesia: Cardiac output (L.)	Induction: Systolic BP (mm. Hg)	Induction: Diastolic BP (mm. Hg)	Induction: Pulse rate (min.)	Induction: Stroke volume (ml.)	Induction: Cardiac output (L.)	Maintenance: Systolic BP (mm. Hg)	Maintenance: Diastolic BP (mm. Hg)	Maintenance: Pulse rate (min.)	Maintenance: Stroke volume (ml.)	Maintenance: Cardiac output (L.)	End of anaesthesia: Systolic BP (mm. Hg)	End of anaesthesia: Diastolic BP (mm. Hg)	End of anaesthesia: Pulse rate (min.)	End of anaesthesia: Stroke volume (ml.)	End of anaesthesia: Cardiac output (L.)
	20	M	O	2	60	dMC	100	62	86	72	6.1	108	70	96	67	6.4	110	68	90	70	6.3	112	62	76	78	5.8
	26	F	M	1	145	G	100	68	98	62	6.0	120	88	102	50	8.2	112	84	112	50	5.7	120	78	110	61	6.8
	28	F	M	1	50	G	108	60	118	72	8.5	104	60	122	71	8.7	108	68	122	64	7.8	120	70	110	68	7.5
	32	F	O	2	135	dMC	90	60	70	61	4.3	110	76	72	54	3.9	110	76	74	54	4.0	110	72	82	58	4.7
	36	F	M	1	90	dMC	110	70	100	58	5.8	100	70	110	53	5.8	108	72	90	55	5.0	112	80	74	48	3.5
	37	F	M	1	45	dMC	138	90	100	50	5.0	126	92	102	41	4.2	112	90	86	37	3.1	110	84	84	41	3.4
	40	F	M	1	155	dMC	120	78	92	51	4.7	104	70	96	52	5.0	110	78	80	46	3.7	110	76	80	49	4.0
	41	F	M	1	155	dMC	100	60	72	61	4.3	106	64	86	59	5.1	100	60	72	61	4.3	100	60	90	61	5.5
	41	F	M	1	165	dMC	120	90	78	38	2.9	126	90	74	41	3.0	108	74	96	49	4.6	126	80	92	51	4.7
	43	F	L	1	95	G	138	82	96	53	5.1	128	82	98	48	4.7	104	72	96	47	4.6	138	90	102	45	4.6
	43	F	M	1	100	G	110	80	100	42	4.2	108	78	100	44	4.4	102	76	110	43	4.7	100	70	110	49	5.3
	44	F	M	1	95	G	106	74	72	47	3.3	116	76	96	50	4.8	106	70	108	52	5.6	110	60	100	64	6.4
	45	F	M	2	75	G	120	80	86	48	4.1	132	94	96	38	3.7	130	98	110	35	3.9	136	100	110	35	3.9
	45	F	O	2	145	G	124	86	90	42	3.7	120	82	92	44	4.1	122	90	92	36	3.3	122	86	78	42	3.2
	46	F	M	1	105	dMC	128	80	70	50	3.5	130	82	72	49	3.5	142	88	68	49	3.3	168	100	72	48	3.5
	47	F	O	2	100	G	100	68	72	55	3.9	110	70	84	58	4.3	122	82	100	44	4.4	128	84	100	45	4.5
	47	F	M	1	95	G	108	80	94	40	3.7	116	80	108	44	4.7	124	86	120	42	5.0	130	90	100	40	4.0
	50	F	M	2	125	dMC	130	70	98	59	5.8	136	84	98	47	4.6	142	98	80	35	2.7	140	92	76	41	3.1
	50	F	M	1	130	G	92	60	80	48	4.1	108	82	96	37	3.6	100	72	102	40	4.1	102	80	100	32	3.2
	54	M	M	3	165	dMC	148	80	140	55	7.7	146	88	124	45	5.6	140	86	100	45	4.5	130	82	100	44	4.4
	54	F	M	2	205	G	150	86	82	49	4.0	154	88	80	49	3.9	130	86	82	40	3.2	122	76	90	47	4.2
	54	M	O	2	75	G	130	80	82	47	3.9	142	84	84	49	4.1	124	68	104	57	6.0	130	64	90	63	5.7
	55	F	O	2	105	G	138	70	92	61	5.5	148	102	100	31	3.1	136	100	90	27	2.4	132	102	92	23	2.0
	56	F	L	2	60	G	160	100	90	38	3.5	148	100	90	32	3.0	130	90	84	35	3.0	130	90	100	35	3.5
	56	F	M	2	190	G	120	60	80	62	5.0	120	62	100	60	6.0	114	64	100	54	5.4	124	70	80	53	4.2
	57	F	O	3	250	G	118	70	80	49	4.0	106	60	90	55	5.0	104	70	90	43	4.0	106	70	80	45	3.6
	57	M	O	2	225	G	116	78	82	41	3.5	116	78	86	41	3.6	108	92	92	20	1.8	140	90	100	39	3.9
	59	M	M	3	110	G	148	80	82	58	4.7	124	72	110	48	5.3	120	80	108	38	4.0	138	90	94	36	3.3
	61	F	O	3	195	G	84	60	92	41	3.7	94	66	92	40	3.7	122	90	94	27	2.4	128	92	100	27	2.7
	62	F	O	3	290	G	146	72	110	57	6.3	150	78	110	55	6.0	136	82	114	41	4.7	122	72	106	45	4.8
	64	F	O	2	75	dMC	170	100	90	38	3.4	184	106	94	39	3.6	206	112	82	43	3.3	216	112	82	47	3.9
	66	F	O	2	230	G	120	90	100	25	2.5	108	74	100	35	3.5	110	70	92	40	3.7	130	84	90	35	3.1
	67	F	O	2	145	G	120	80	100	34	3.4	100	70	106	35	3.7	160	96	106	36	3.8	164	100	104	33	3.3
	71	M	M	3	250	dMC	190	90	80	55	4.4	162	84	76	47	3.6	144	88	76	34	2.5	170	110	86	23	1.7
	71	M	O	3	150	dMC	128	90	78	49	3.9	100	76	74	25	1.7	116	76	76	33	2.5	108	70	82	36	2.9
	72	F	O	4	195	G	130	90	120	24	2.8	120	70	110	41	4.5	160	90	100	40	4.0	170	110	100	23	2.3
	73	M	M	2	170	G	120	86	100	24	2.4	126	82	82	30	2.2	124	84	114	27	2.9	138	90	118	27	3.1
	73	F	M	3	330	G	120	70	90	40	3.6	120	68	84	43	3.6	106	64	80	39	3.0	110	70	84	36	2.9
	74	F	M	4	130	dMC	140	80	110	39	4.3	118	68	94	41	3.8	106	68	88	35	3.0	112	70	90	36	3.1
	75	F	M	3	80	G	150	90	82	33	2.5	170	98	94	34	3.1	164	106	96	22	2.0	180	108	100	28	2.8
	76	F	M	1	135	dMC	128	70	80	43	3.4	116	66	78	41	3.1	110	68	78	36	2.7	116	66	80	41	3.3
	76	M	O	3	60	dMC	180	92	80	44	3.5	164	92	82	37	3.0	184	108	82	29	2.4	198	110	84	34	2.7
	81	F	M	3	80	dMC	104	70	78	28	2.0	90	50	82	42	3.4	100	62	90	34	3.0	122	80	92	26	2.1
	91	M	M	2	170	dMC	160	70	76	50	3.8	126	72	70	30	2.1	148	74	66	39	2.1	168	82	68	40	2.6
Mean	55				140		128	77	90	47	4.2	124	78	94	45	4.3	125	81	93	41	3.8	132	84	92	43	3.9
S.D.							25	11	15	12	1.3	21	12	17	10	1.4	23	13	14	11	1.3	26	15	12	13	1.3
S.E.							4	2	2	2	0.2	3	2	3	2	0.2	4	2	2	2	0.2	4	2	2	2	0.2

TABLE I (*continued*)

D. Spinal Operations in Prone Position (24 patients)

	Age	Sex	Build	Physical state	Anaesthesia time	Muscle relaxant	Before anaesthesia					Induction					Maintenance					End of anaesthesia				
							Systolic BP	Diastolic BP	Pulse rate	Stroke volume	Cardiac output	Systolic BP	Diastolic BP	Pulse rate	Stroke volume	Cardiac output	Systolic BP	Diastolic BP	Pulse rate	Stroke volume	Cardiac output	Systolic BP	Diastolic BP	Pulse rate	Stroke volume	Cardiac output
					(min.)		(mm. Hg)		(min.)	(ml.)	(L.)	(mm. Hg)		(min.)	(ml.)	(L.)	(mm. Hg)		(min.)	(ml.)	(L.)	(mm. Hg)		(min.)	(ml.)	(L.)
	14	M	M	2	180	dMC	110	80	110	61	6.7	116	78	106	66	7.0	112	84	76	57	4.4	112	88	80	53	4.2
	14	M	M	2	300	G	130	90	110	59	6.5	118	90	140	54	7.6	120	90	120	55	6.6	110	80	118	61	7.7
	21	M	L	2	115	dMC	110	70	80	68	5.4	110	70	80	67	5.3	114	82	82	56	4.6	120	90	82	50	4.1
	22	F	M	1	185	G	120	74	82	68	5.5	116	72	110	68	7.5	108	80	96	50	4.8	110	80	98	56	5.5
	23	M	M	1	190	G	110	70	72	66	4.7	100	70	78	61	4.7	104	78	94	55	5.2	114	90	82	46	3.6
	28	F	O	2	225	dMC	88	60	68	63	4.3	92	62	68	62	4.3	96	74	72	51	3.5	102	64	80	66	5.2
	28	M	M	1	240	dMC	118	80	60	56	3.4	120	82	60	54	3.2	118	94	76	40	3.0	116	86	74	48	3.5
	30	M	O	2	370	G	100	60	80	67	5.3	100	62	80	65	5.2	104	72	94	56	5.3	92	66	84	57	4.8
	35	M	M	1	350	G	108	78	74	49	3.6	112	80	124	49	6.0	116	82	122	48	5.8	112	82	128	47	6.0
	39	F	O	2	105	dMC	128	78	82	56	4.4	128	78	84	57	4.8	130	90	77	45	3.4	140	100	82	39	3.1
	39	M	M	2	330	dMC	90	60	64	57	3.3	92	62	68	56	3.9	98	66	74	54	4.0	96	60	72	60	4.3
	42	M	M	2	175	dMC	130	90	80	44	3.6	90	76	70	38	2.6	122	96	78	35	2.6	118	92	78	34	2.6
	42	M	M	1	225	G	128	80	90	53	4.8	130	80	90	54	4.9	118	90	84	36	2.6	110	82	92	41	3.8
	45	M	M	1	340	dMC	140	80	90	56	5.2	140	90	96	46	4.4	118	82	64	44	2.7	116	80	58	45	2.6
	45	M	M	1	320	dMC	102	68	60	52	3.2	102	68	60	51	3.1	114	91	78	32	2.4	110	80	76	42	3.1
	47	M	O	2	85	dMC	116	80	72	44	3.0	116	84	72	39	2.8	118	70	76	56	4.2	120	64	68	63	4.3
	47	F	L	1	90	dMC	130	80	104	51	5.3	130	80	104	51	5.3	112	74	82	48	3.9	110	78	68	43	2.9
	50	M	O	2	305	dMC	84	54	60	53	3.2	84	52	60	57	3.4	112	82	66	37	2.5	110	80	58	39	2.2
	50	M	O	3	410	dMC	110	68	80	52	4.1	98	66	80	48	3.8	90	54	88	57	5.0	90	50	100	61	6.1
	51	M	M	1	180	dMC	100	70	60	43	2.6	100	72	72	42	3.0	90	68	76	41	3.1	92	64	78	46	3.6
	53	F	O	3	435	G	110	78	82	38	2.9	102	80	78	32	2.4	110	86	104	31	3.2	108	87	118	28	3.2
	60	M	O	2	275	G	120	70	90	48	4.3	120	70	100	48	4.8	108	74	82	37	3.0	90	50	80	55	4.4
	62	F	M	1	135	dMC	120	92	80	23	1.8	120	90	100	25	2.5	132	94	95	27	2.5	138	96	108	27	2.8
	62	F	O	3	320	dMC	150	96	100	33	3.3	134	90	80	32	2.5	116	90	86	23	1.9	112	84	92	27	2.5
Mean	40				245		115	75	80	53	4.1	111	75	86	51	4.4	112	81	85	45	3.8	110	78	86	47	4.0
S.D.							16	11	15	11	1.5	15	10	21	12	1.6	11	10	15	11	1.2	13	14	18	11	1.4
S.E.							3	2	3	2	0.3	3	2	4	2	0.3	2	2	3	2	0.3	3	3	4	2	0.3

TABLE I (*continued*)

E. MISCELLANEOUS SUPERFICIAL OPERATIONS IN SUPINE HORIZONTAL POSITION (16 PATIENTS)

							Before anaesthesia					Induction					Maintenance					End of anaesthesia				
	Age	Sex	Build	Physical state	Anaesthesia time (min.)	Muscle relaxant	Systolic BP (mm. Hg)	Diastolic BP (mm. Hg)	Pulse rate (min.)	Stroke volume (ml.)	Cardiac output (L.)	Systolic BP (mm. Hg)	Diastolic BP (mm. Hg)	Pulse rate (min.)	Stroke volume (ml.)	Cardiac output (L.)	Systolic BP (mm. Hg)	Diastolic BP (mm. Hg)	Pulse rate (min.)	Stroke volume (ml.)	Cardiac output (L.)	Systolic BP (mm. Hg)	Diastolic BP (mm. Hg)	Pulse rate (min.)	Stroke volume (ml.)	Cardiac output (L.)
	16	F	M	1	80	G	120	80	118	65	7.7	116	76	120	67	8.0	124	86	126	59	6.3	130	84	120	65	7.8
	17	M	M	1	170	dMC	106	60	60	81	4.7	94	58	72	76	5.4	92	60	70	72	5.1	96	64	70	70	4.9
	18	M	M	2	280	dMC	112	60	74	80	6.1	110	64	78	76	5.9	100	58	98	79	7.7	100	60	100	75	7.5
	22	F	M	1	175	dMC	110	70	80	67	5.3	110	68	78	70	5.5	112	76	80	61	4.9	120	84	88	56	4.9
	41	F	M	1	195	G	110	88	92	36	3.1	110	90	96	33	3.1	116	90	108	37	3.8	116	92	110	33	3.7
	46	M	O	2	70	dMC	128	90	70	41	2.8	128	90	78	39	3.0	130	86	78	45	3.5	136	88	82	46	3.8
	48	F	M	2	110	dMC	140	80	72	55	3.9	130	82	82	47	3.7	132	90	80	39	3.1	140	92	88	40	3.6
	49	F	M	1	170	dMC	100	60	96	57	5.4	118	80	90	49	4.4	124	90	80	35	2.7	106	76	80	42	3.4
	50	M	O	2	110	dMC	128	94	88	30	2.8	140	96	108	35	3.7	142	94	72	39	2.8	148	96	70	40	2.8
	54	M	M	1	40	dMC	110	80	70	37	2.6	110	80	70	36	2.5	118	84	90	36	3.2	120	86	80	35	2.8
	62	M	M	1	155	dMC	128	70	80	50	4.2	120	74	84	43	3.2	124	70	78	49	3.9	140	86	84	39	3.2
	64	F	M	2	115	G	170	102	68	35	2.0	154	90	70	41	2.9	166	114	90	32	2.8	152	110	92	20	1.7
	64	F	O	2	110	G	128	82	78	35	2.6	128	80	74	39	2.5	170	104	112	33	3.7	180	110	92	33	3.0
	71	M	M	3	95	G	100	80	90	21	2.0	106	88	102	16	1.6	108	86	120	23	2.7	106	82	130	21	2.7
	71	M	M	4	155	dMC	158	110	94	16	1.4	120	60	100	53	5.3	130	80	112	36	4.0	140	80	118	41	4.8
	74	F	O	4	150	dMC	160	100	80	27	2.1	140	90	86	28	2.4	140	98	86	19	1.6	150	100	90	23	2.0
Mean	48				136		126	82	82	46	3.7	121	79	87	47	4.0	113	85	93	43	3.9	130	87	94	43	3.9
S.D.							22	15	14	20	1.8	15	12	15	18	1.7	21	15	18	17	1.5	23	14	18	17	1.7
S.E.							5	4	3	5	0.1	4	3	4	4	0.1	5	4	5	4	0.1	6	3	4	4	0.1

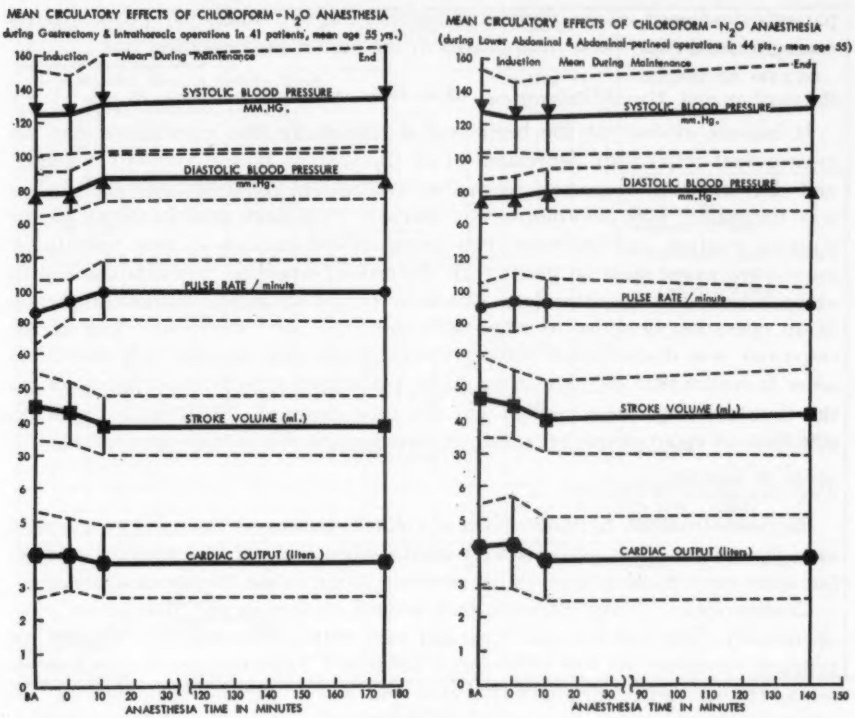

FIGURE 1

gastrectomy and/or intrathoracic operations, and those who had lower abdominal operations.

There was little alteration in the systolic and diastolic blood pressure. The pulse rate usually rose slightly. This rise was most often in response to either intravenous gallamine or atropine, which blocked the tendency toward bradycardia that is seen characteristically with chloroform. The only significant change was a moderate reduction in the estimated stroke volume, while the cardiac output decreased slightly in a few patients.

There was clinical and ECG evidence of moderate to severe heart disease in 24 patients, of whom 11 had a previous history of coronary thrombosis or cerebral vascular accidents, and three others who had a history of congestive heart failure. One of these patients had circulatory difficulties during induction of anaesthesia and again postoperatively. Another had circulatory difficulties five days after recovery from anaesthesia. These two patients died and will be mentioned in detail below. The other 22 patients had an uneventful course.

Cardiac arrhythmias were almost completely absent during this study. Two patients had auricular fibrillation and two patients had bundle branch block preoperatively. They had a smooth recovery from anaesthesia and surgery. Two

patients developed intermittent extrasystoles and two others had coupled beats during anaesthesia. These disappeared at the end of the operation.

Respiration and Muscle Relaxation

It became evident at the beginning of this study that chloroform was the most potent respiratory depressant of all the volatile agents studied heretofore, and that augmenting muscle relaxation was seldom required after the patient was intubated, and chloroform was started. This held true for most of the patients studied, and indicated two necessary precautions in long operations: muscle relaxants must be given with discretion, especially towards the end of an operation; and the chloroform should be turned off shortly before completion of an operation in order to allow sufficient time for "wash out." Use of the respirator was discontinued before closure of the skin incision was started in order to ensure that the patient would have adequate spontaneous respiration by the time dressings were applied and the tube removed. No difficulty with resumption of spontaneous breathing occurred when this routine was followed.

Post-anaesthetic Morbidity

Recovery from the hypnotic effect of chloroform was not as rapid as was seen after halothane. Most patients were awake when they left the operating room, but often went to sleep again in the recovery room, unless they were stimulated.

Cardiovascular. Three patients had serious cardiovascular difficulties postoperatively. The first was a 71-year-old man with a fractured hip. Besides his primary condition, he had myocardial ischaemia, hypertension, severe emphysema, chronic bronchitis, and diabetes. He was a chronic alcoholic. At the admission examination, he complained mostly of pain in the abdomen (which apparently began just before the hip injury), but this was not taken seriously since abdominal examination did not reveal any localized tenderness or rigidity. After induction of anaesthesia and movement to an orthopaedic table, his blood pressure fell sharply. Positioning and manipulation of the hip were delayed until his condition improved. The anaesthetic and operative course was uneventful thereafter. Postoperatively he had respiratory and circulatory difficulty. Raising secretions was a problem, and he continued to complain of abdominal discomfort. On the second postoperative day his condition rapidly deteriorated in spite of vigorous therapy, and death ensued. At post-mortem, mesenteric thrombosis of recent origin was found, and the lungs showed bilateral bronchopneumonia (Fig. 2).

The second patient was a 57-year-old, very obese male with fever and tachycardia, who had a cholecystectomy from which anaesthetic and surgical recovery appeared to be rapid and smooth. On the third postoperative day he developed severe substernal pain and died suddenly. No post-mortem was obtained, but it was assumed that this death was caused by an acute coronary occlusion or a pulmonary embolus (Fig. 3).

The third patient, a 78-year-old male who had a normal ECG preoperatively, and appeared fit for his age, developed dyspnoea, chest pain, and hypotension while walking in the hospital corridor five days after a cholecystectomy. He was

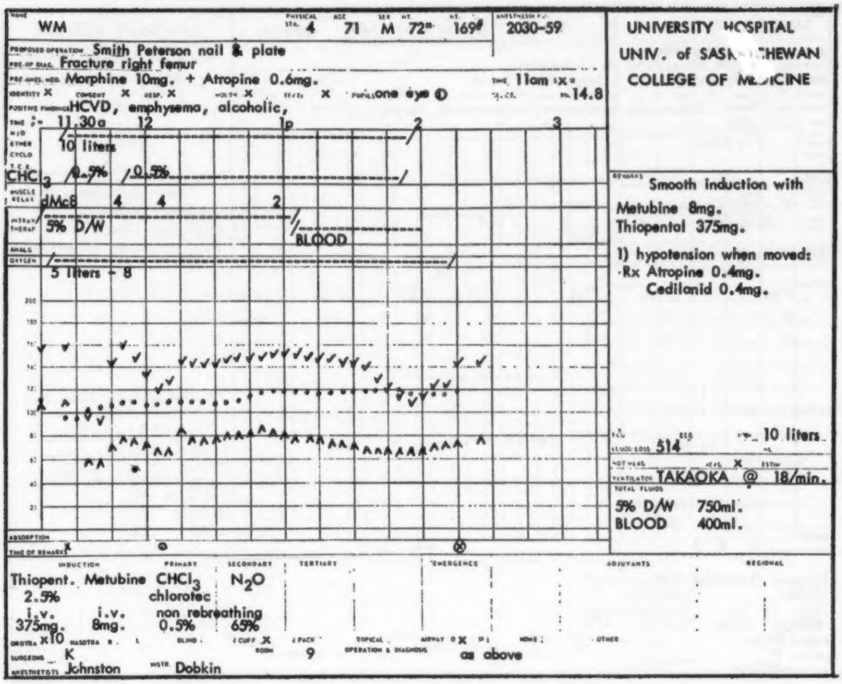

FIGURE 2

returned to bed, given morphine, digoxin, oxygen, and anticoagulent therapy. ECG some hours later showed evidence of acute myocardial infarction. After three weeks on bed rest, he recovered completely and was discharged from hospital. He has been well since (three months later) (Fig. 4).

Gastrointestinal. Nausea and/or vomiting occurred in 43 patients (28 per cent) in the postoperative period. Most of these responded well to perphenazine. In a few cases these symptoms recurred after the patient was returned to the ward from the recovery room. In eight of these 43 patients, the initial onset of nausea and vomiting occurred several days after the operation, and after food or water was first taken by mouth. Postoperative vomiting that might be attributed to the anaesthetic occurred therefore in 23 per cent of the patients.

Jaundice. Clinical jaundice was present in nine patients during the postoperative period. Five of these were admitted to hospital with jaundice. In four of them, the jaundice subsided after operation. The fifth patient, a female aged 73 years, was investigated for six days, and then had an abdominal exploration, liver biopsy, and common bile duct exploration. A clinical diagnosis of chronic cholangitis, acute pancreatitis, and multiple cysts of the liver, was made. She had an uneventful course during the first five days after the operation, and her jaundice subsided. She then developed acute abdominal distension and vomiting.

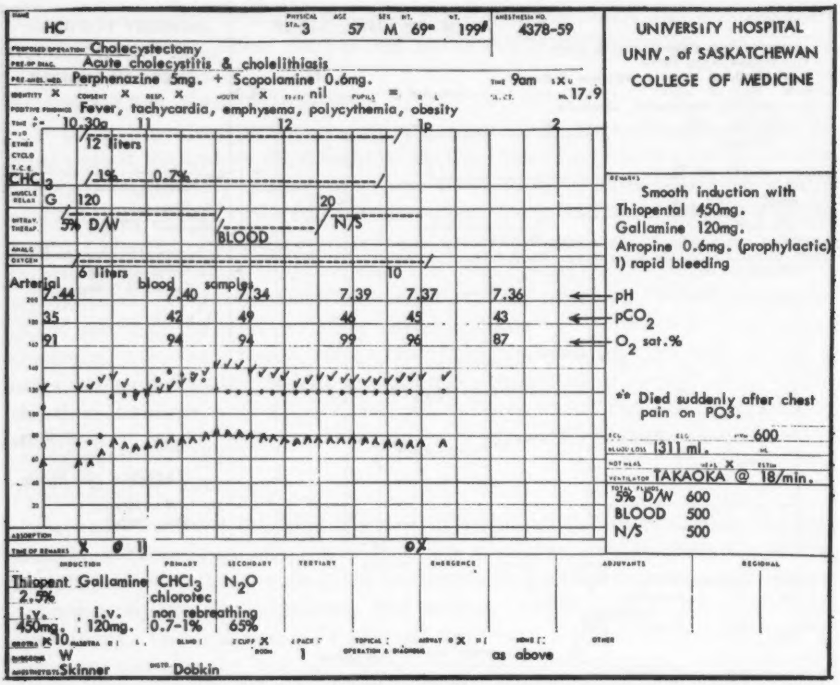

FIGURE 3

This was thought to be due to an ileus, or to a subhepatic abscess. Her condition degenerated rapidly, and she died the next day. At post-mortem a bile peritonitis was found, and was considered the primary cause of death.

The other four patients developed jaundice postoperatively. In one very obese male patient, aged 61 years, it appeared two days after a gastrectomy operation of three hours duration. No blood was given during this operation because his preoperative haemoglobin was 16.3 gm. per cent and blood loss was slight. The jaundice gradually increased for four days, and then disappeared by the ninth postoperative day. During the early postoperative period the patient developed tachycardia, and his haemoglobin fell from 15 gm. (immediately after surgery) to 11 gm. a few days later, when it was also observed that he passed a tarry stool. Blood transfusions were given to restore the blood volume. He was discharged from hospital on the fifteenth postoperative day in good condition. It is possible that the chloroform was a cause of his jaundice although jaundice is not an uncommon occurrence after a gastrectomy, especially if marked bleeding continues postoperatively, and if the patient is obese.

The second patient was a male, 59 years of age, who had a history of intermittent jaundice. At a previous operation a few years earlier, attempted chole-

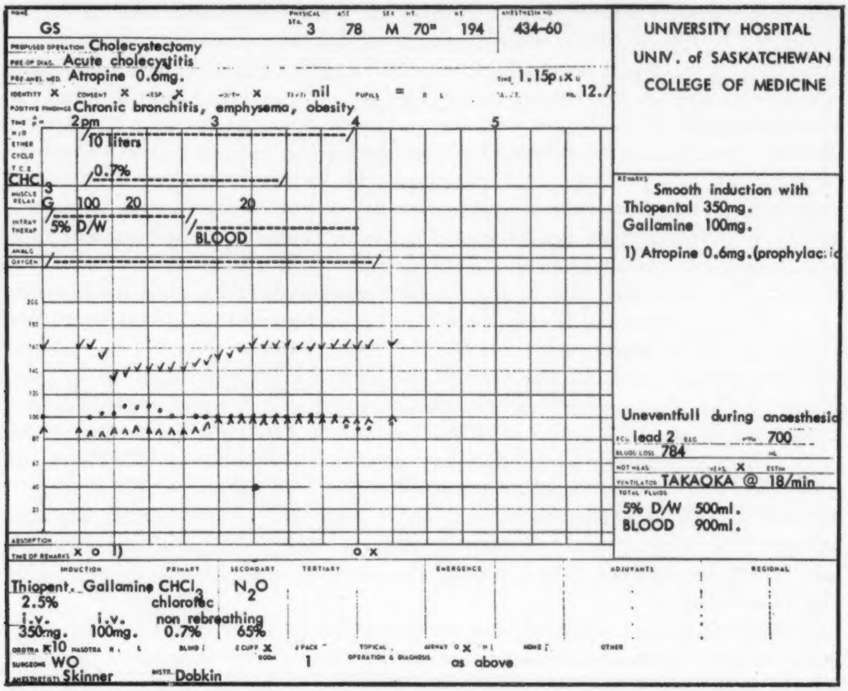

FIGURE 4

cystectomy was abandoned because of technical problems and the gall bladder was drained. He had a prolonged and difficult recovery. In the present instance, cholecystectomy and common bile duct exploration were done during an intricate 4-hour operation. The measured blood loss at this operation was a little in excess of 500 ml. No blood was replaced because his preoperative haemoglobin was 16.2 gm. Later in the recovery room it was felt that he needed blood, and a transfusion was administered. He had a stormy postoperative course again, owing to development of a subhepatic abscess and duodenal fistulae, and several blood transfusions were given as supportive therapy. On the tenth postoperative day he developed slight jaundice. After the abscess was drained and the fistulae were closed at subsequent operations, complete recovery of this patient was slow. The jaundice that developed was undoubtedly due to the surgical complications, and multiple blood transfusions.

The third patient was an obese 60-year-old male with carcinoma of the stomach. He had lost 20 lb. in a short period, and was receiving cortisone for treatment of arthritis. During a $6\frac{1}{2}$-hour operation, a total gastrectomy, splenectomy, and Roux en-Y anastomosis was done. Bleeding was difficult to control during the operation. Measured blood loss was 1,664 ml. and the estimated additional loss

was in excess of 1,000 ml. Blood transfusions were started one hour after the beginning of the operation when it was observed that bleeding was excessive, even though his initial haemoglobin was 16.0 gm. A total of 2,850 ml. of blood was administered during the operation. The patient recovered promptly from the anaesthetic and his vital signs were stable. On the first postoperative day he had difficulty coughing up secretions. His upper airway had to be suctioned frequently to stimulate him to cough and to remove the secretions because he was not co-operative. On the second postoperative day his temperature rose to 101°F., and there were decreased breath sounds in the right chest. An endotracheal tube was passed and tracheobronchial suctioning produced a large amount of sticky mucus. This improved the breath sounds considerably. In spite of vigorous physiotherapy, bronchial breath sounds and rales returned and his temperature spiked to higher levels each day. On the sixth postoperative day his general condition deteriorated. On the seventh day jaundice appeared, and he died the following day. Post-mortem examination revealed that the patient had diffuse carcinoma of stomach and widespread secondary carcinoma. The abdominal cavity had generalized fibrinopurulent peritonitis. There was mucopurulent bronchitis and right bronchopneumonia. The liver and kidney showed moderate and slight fatty degeneration respectively. Generalized arteriosclerosis was also evident. The primary cause of death in this case was fibrinopurulent peritonitis and bronchopneumonia. The jaundice was terminal and probably unrelated to the anaesthetic.

The fourth patient was a 56-year-old female who had a recurrent leiomyosarcoma removed from the transverse mesocolon and a total colectomy during a 3-hour operation. Measured blood loss during the operation was only 238 ml., but on account of her anaemia (preoperative haemoglobin 11.5 gm.) she was given a blood transfusion during the operation. She recovered promptly from the anaesthetic. On the fifth postoperative day she became slightly jaundiced (total bilirubin 4.8 mg. per 100), but felt well. The jaundice disappeared after one week, and she was discharged from hospital in good condition 16 days after her operation. The slight jaundice in this case may have been due to the chloroform anaesthetic and/or to the blood transfusion.

Postoperative Mortality

In addition to the four deaths mentioned above, one other patient who received chloroform anaesthesia died postoperatively. This was a 59-year-old male with myocardial ischaemia (previous history of myocardial infarction), hypertensive heart disease, and asthma, who had an abdominal operation 2 hours in duration. He had carcinoma of the rectum with wide extension that could not be removed, and a palliative left colostomy was done. The patient recovered from anaesthesia promptly, and was apparently well for four days, then developed marked abdominal distension and bronchopneumonia. He died the following day. At post-mortem, widespread infarction of the colon, acute inflammation of the small bowel, and acute bronchopneumonia were found. This death appeared to be due to surgical complications (Fig. 5).

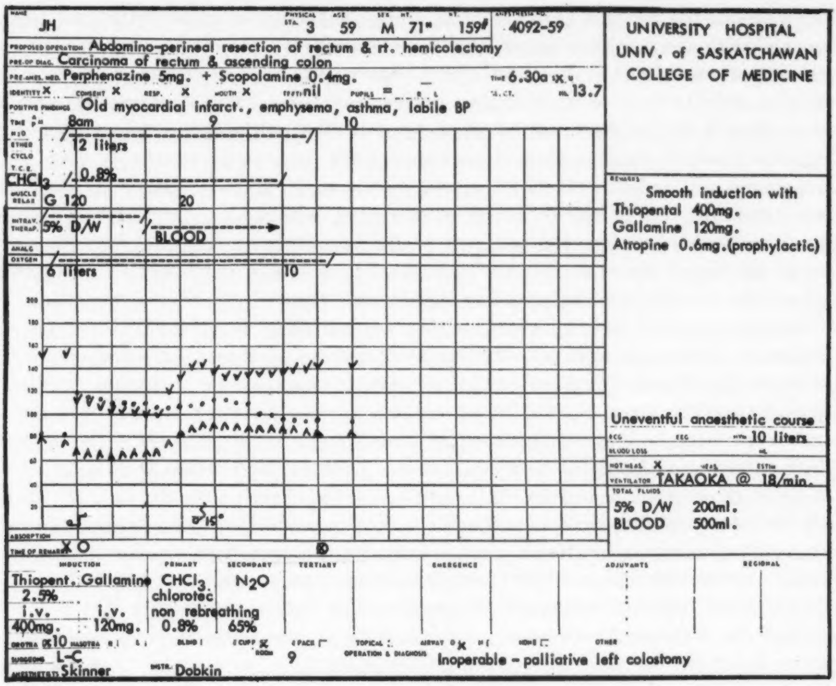

FIGURE 5

Discussion

Over ten years ago it was concluded from a detailed re-evaluation of chloroform that this agent does not deserve to be abandoned as a surgical anaesthetic (4, 5). Although only a few reports on the clinical use of chloroform have been published recently (6, 7, 8), the opinion expressed above is supported by several anaesthetists who have continued to use chloroform even after the introduction of halothane—whose advantage over chloroform still appears to be quite nebulous (9).

The bad press which chloroform has had may be said to have started with the report of Hannah Greener's fate (10). In spite of the Hyderabad Commissions (1888 and 1889) this culminated in the opinion expressed by the Committee on Anaesthesia of the American Medical Association, which stated in 1912 that the "use of chloroform for major operations is no longer justifiable . . ." (11). Since then, anaesthetists who have persisted in using chloroform have been on the defensive because postoperative morbidity is readily blamed on this ideal scapegoat. Despite this, its defenders continue to believe that it is a useful anaesthetic agent which has been inordinately maligned (12).

In an erudite address entitled "The Natural History of Error," William Bean opened with the pertinent question: "Who has not wondered at man's marvellous talent for making mistakes and then perpetuating them? The capacity of the human mind to deceive itself knows hardly any limit." Citing numerous errors that have been perpetuated, he reminds us of Milton's words: "Error supports custom, custom countenances error: and these two between them, with the numerous and vulgar train of their followers, envy and cry down industry of free reasoning, under the terms of humour and innovation. Truth never comes into the world, but like the bastard, to the ignominy of him that brought her forth; till Time, the mid-wife, rather than the mother of truth, hath washed and salted the infant, and declared her legitimate" (13).

Several areas of anaesthetic teaching are suffering from the same type of prejudice as the attempts to re-evaluate chloroform—for instance, that of direct artificial respiration (oral resuscitation). The antagonists in both these controversies take the same bigoted line of reasoning: the agent or method was tried many years ago, and was superseded by something new, which is therefore better. With a few refinements in technique, direct artificial respiration is now proving to be an efficient and a widely applicable method of reviving the dying (14). With a little tolerance and some very careful clinical application, undoubtedly chloroform can also again become a useful anaesthetic agent with valid indications, which need not be replaced by modern agents but can be used along with them.

Middleton reported extensive experience with chloroform during World War II, and he feels that adequate atropinization of the patient is an important prerequisite for smooth chloroform anaesthesia (15). Armstrong Davison has observed that maintenance of chloroform anaesthesia is further facilitated if the patient is adequately premedicated with a phenothiazine derivative, in order to produce effective sedation and reduce the concentration of chloroform required for surgical anaesthesia (7). The general principles for maintaining a clear airway and avoiding hypoxia and hypercarbia certainly apply to the use of chloroform anaesthesia, as they would for any other potent anaesthetic agent (16, 17). In addition, much effort has been directed in the past few years to devising means for accurate regulation of the concentration of this agent in the anaesthetic circuit (18, 19).

In comparison with other halogenated anaesthetic vapours, the effect of chloroform on circulatory dynamics and on cardiac rhythm, even in the presence of epinephrine, is not more dangerous than that of the other agents in common and extensive use. Protection against cardiac arrhythmias afforded by a phenothiazine derivative is as reliable with chloroform as with cyclopropane, halothane, the halothane–ether azeotrope, and trichloroethylene. The most important precaution that must be emphasized with all these agents is the maintenance of adequate pulmonary ventilation throughout the time of their administration, and until almost complete washout from the patient's blood stream has been accomplished (20, 21). The reduction in cardiac arrhythmias and circulatory difficulties has been shown with these simple practices alone (22, 23).

In clinical use with identical methods of administration, the hypnotic effect of chloroform was only slightly less potent than Fluothane and slightly more

potent than the Fluothane–ether azeotrope (17, 24, 25, 26). Dogs, on the other hand, are more sensitive to this effect of chloroform (21), whereas Mørch and Jobgen have noticed that there is very little difference in the hypnotic potency of Fluothane and chloroform in small animals (27).

Muscle relaxation was better with chloroform than with either Fluothane or the Fluothane–ether azeotrope. Muscle relaxants did not appear to cause hypotension with chloroform, as was sometimes seen with Fluothane. The circulatory effect of chloroform resembled more the Fluothane–ether azeotrope than Fluothane—that is, chloroform was less likely to cause hypotension than Fluothane. There was a greater tendency to prolonged tachycardia when gallamine was administered for endotracheal intubation followed by chloroform than when followed by Fluothane or Fluothane–ether azeotrope. For this reason, it was considered preferable to use dimethyl-d'tubocurarine with chloroform instead of gallamine, and to use atropine to counteract bradycardia when it occurred.

Just as Goodman Levy's words made the cardiac effects of chloroform a hazard to be feared, so such reports as those of Whipple and Sperry, and, more recently, those of Sheehan have focused attention on the toxic effects of chloroform on the liver (28, 29, 30). Both these effects have been studied unrealistically. With regard to the liver, in most of the animal studies quoted, either no attempt was made to provide the usual supportive therapy during anaesthesia (intravenous fluids and augmented pulmonary ventilation) or no attempt was made to administer a regulated dose of chloroform that would be within the clinically useful range. In some of the studies the animals were starved for two to three days before an experiment, in order to augment the deleterious effects of chloroform on the liver. Such procedures would show diethyl ether and halothane in a bad light also. The dictum "chloroform poisoning is synonymous with chloroform anaesthesia" is logical only in the same sense as asphyxia and starvation may be synonymous with death (31, 32). The standards recommended presently for evaluating the effect of chloroform or any other halogenated anaesthetic agent on the liver of animals are of limited clinical application unless appropriate steps are taken to assure proper nutrition and to augment pulmonary ventilation —for these are essential prerequisites in the safe administration of any potent anaesthetic to the depth that is required for prolonged surgical anaesthesia (33, 34, 35).

Bunker has made the apt clinical observation that there are no differences in the effect on the liver that can be attributed to an anaesthetic agent or technique. Rather, the operative procedure and the degree of preoperative liver damage have the more marked effects on both the postoperative disturbances in liver function tests and the clinical result. As far as the liver is concerned, the choice of anaesthetic agent is of less importance than careful preoperative preparation, adequate oxygenation during the operation and postoperatively, and the use of fresh blood transfusions (36).

The administration of transfusions of stored bank blood is certainly to be implicated in a variety of metabolic and blood-clotting defects which harass both anaesthetist and surgeon during a major operation and during the postoperative recovery period. It is well known that disturbances such as jaundice

and uncontrollable capillary bleeding are caused by bank blood transfusions, especially when used for intrathoracic operations and those involving the portal circulation (37, 38, 39). This effect of administering stored blood undoubtedly occurs to a varying degree in most operations.

One further form of postoperative disease is beyond the control of the anaesthetist, and is often related to anaesthetic morbidity rather than to inherent metabolic derangements. An ever-growing proportion of major operations are performed on patients who are grossly obese. In the present study, 38 per cent of patients were definitely overweight, according to life insurance standards (40, 41, 42). A wide range of serious problems arise insidiously when anaesthesia is administered to an obese patient (43). Not the least of these is aggravation of the condition of the liver. Zelman has shown that the apparently healthy obese person has anatomical damage of the liver that is similar to that of the chronic alcoholic. Many have impaired glucose tolerance, and bromsulphalein retention is abnormal in all such individuals even when they are "well" (44). Any clinical reports on the effect of supposedly hepatotoxic anaesthetic agents must be analysed, therefore, in the proper perspective whenever the patient is obese.

It is interesting to note some of the morbidity and mortality reports which are now appearing, that relate toxic changes in the liver to halothane. Barton gives no indication of other possible causes of the jaundice in his patients who received halothane (45, 46). Virtue and Paine, in a death report of a patient who had received halothane, imply that the acute yellow atrophy of the liver ound at post-mortem could have been due to delayed halothane poisoning (47). These two reports contain some faulty reasoning as was noted above. The latter death was in an obese patient with an obvious history of liver disease. She had several episodes of severe hypotension during anaesthesia, which could have markedly reduced liver blood flow to a level that would cause acute prolonged hepatic anoxia. These factors alone might account for the post-mortem changes observed in the liver; so why imply that halothane alone was the culprit, in the way that chloroform was blamed in the past? With a little detective work and some logical reasoning, many factors could explain the liver damage without specifically implicating the particular anaesthetic agent that happened to be administered.

In carrying out the present study, every precaution was taken that was known to facilitate management of the anaesthetic. Nevertheless, there were many factors—the general condition of the patient, the skill and judgment of the surgeon, the availability of fresh blood, the care and attention of the anaesthetist, and the will to live by the patient, especially when he knew that he was suffering from a very serious illness—which were not all in the hands of the anaesthetist, and were mainly beyond his control. Even so, the morbidity in this group of 154 patients was not significantly different from that of other patients who were undergoing similar operations by the same surgeons, but with other anaesthetic agents.

The general surgical mortality during this study, in all major and minor procedures, except neurosurgical, paediatric, and cardiovascular operations, was 3 per cent (56 deaths in 1,839 patients). The mortality rate among patients who

received chloroform anaesthesia for major operations only was approximately the same (5 deaths in 154, or 3.2 per cent).

The postoperative mortality among the patients who underwent cholecystectomy, gastrectomy and bowel resection, and related operations during this study was reviewed in detail, and is shown in Table II. The mortality rate was 5.2 per cent for the chloroform group, and 15 per cent for the other group. This difference was too striking to have been due to chance alone; yet, in none of the cases that did not receive chloroform, did the surgeon question the anaesthetic selected, whereas the use of chloroform was criticized, in each of the deaths described. However, in none of these (with or without chloroform) was the anaesthetic agent finally considered as the primary or major contributing cause of death.

TABLE II

POSTOPERATIVE MORTALITY
(JUNE, 1959, TO FEBRUARY, 1960)

Operation	No. of patients	Anaesthetic		Deaths	
		Chloroform	Other	Chloroform	Other
Gastrectomy and related procedures	65	27	38	1	4
Cholecystectomy and related procedures	72	29	43	2	5
Bowel resection and related procedures	56	22	34	1	7
TOTALS	193	78	115	4	16

On the basis of the cases reported, this study supports the opinion that chloroform is a potent agent which must be vaporized in a precision system, and when administered with care and attention to the necessary prophylactic and therapeutic measures, it provides satisfactory operating conditions without increasing postoperative morbidity or mortality.

SUMMARY AND CONCLUSIONS

Chloroform with nitrous oxide and oxygen was administered to 154 patients during major operations, employing a precision non-rebreathing system with a calibrated vaporizer. Artificial respiration was provided with a pressure regulated ventilator designed by Takaoka, and pulmonary ventilation was set to the requirements of the individual patient. Smooth maintenance of anaesthesia was accomplished in this system with 0.5 to 1 per cent chloroform, 65 per cent nitrous oxide, and small supplements of muscle relaxant drugs. This method sufficed to produce satisfactory operating conditions without inducing cardiovascular depression. Dimethyl d'tubocurarine was preferred to gallamine as the muscle relaxant, because the latter sometimes caused prolonged tachycardia.

The only alteration in the vital signs that was frequently observed was a slowing of the pulse rate. This was effectively treated with atropine. A moderate reduction in the estimated stroke volume and cardiac output was also observed, but this was of the same degree as was seen with the Fluothane–diethyl ether azeotrope. Cardiac arrhythmias in these cases were significant by their absence even in those patients with serious cardiovascular disease.

Postoperative recovery from anaesthesia was not significantly slower than that observed after Fluothane. The incidence of postoperative nausea and vomiting was somewhat higher than average, but was similar to that seen with other anaesthetics for the particular operations in which it was used. Postoperatively serious cardiovascular depression attributable to the anaesthetic agent alone was not seen. The incidence of postoperative jaundice was regarded prominently because it was expected to occur more often after chloroform than after other anaesthetics, but this was not evident when the data of this study were reviewed. Surgical mortality was not higher after chloroform anaesthesia than after other anaesthetics for similar operations by the same surgeons.

This study shows that chloroform has, in fact, been inordinately maligned as an anaesthetic for major operations. When used with the same care and precision as are expected for other potent agents, it undoubtedly has a place in clinical practice along with the other halogenated anaesthetic vapours.

Résumé

Au cours d'opération majeure, nous avons administré à 154 malades du chloroforme avec du protoxide d'azote et de l'oxygène; nous avons employé un système sans ré-inspiration et un vaporisateur calibré. A l'aide d'un ventilateur à pression réglable, conçu par Takaoka, nous avons pratiqué une respiration artificielle chez ces malades et le volume de la ventilation pulmonaire correspondait aux exigences préétablies de chacun de ces malades. Grâce à ce système, l'anesthésie a été doucement maintenue avec 0.5 à 1% de vapeurs de chloroforme, 65% de protoxide d'azote et de petites doses de myorésolutifs pour compléter. Cela s'est avéré suffisant pour fournir des conditions opératoires satisfaisantes sans provoquer de dépression cardiovasculaire. Comme agent myorésolutif, nous avons préféré la d'tubocurarine à la gallamine, parce que quelquefois cette dernière peut entrainer des tachycardies prolongées.

La seule modification des signes vitaux que nous avons observée a été un ralentissement du pouls. Cette bradycardie a été efficacement corrigée par de l'atropine. Nous avons également observé une légère diminution de l'ondée systolique et du débit cardiaque mais nous avons observé la même chose avec le mélange Fluothane–éther azeotrope. Nous avons été étonnés de n'avoir observé d'arythmie cardiaque chez ces malades même chez des porteurs de maladies cardiovasculaires.

Après l'opération, le réveil n'a pas été plus tardif qu'il n'avait été avec le Fluothane. La fréquence des nausées et des vomissements postopératoires a été un peu plus grande que la moyenne, mais elle différait peu de celle observée avec d'autres agents anesthésiques pour des opérations semblables à celles où il avait été employé. Nous n'avons pas observé de dépression cardiovasculaire sérieuse postopératoire attribuable exclusivement à l'agent anesthésique. Nous avons porté une attention spéciale à la jaunisse postopératoire parce que nous nous attendions d'en observer plus souvent qu'avec l'usage des autres agents anesthésiques mais, au moment de colliger les observations de cette étude, on ne nous a pas signalé cette complication. La mortalité opératoire après l'anes-

thésie au chloroforme n'a pas été plus élevée qu'avec les autres agents anesthésiques pour les mêmes opérations pratiquées par les mêmes chirurgiens.

Cette étude démontre que, en fait, le chloroforme s'est avéré particulièrement mauvais comme agent anesthésique pour des opérations majeures. Mais s'il est employé avec le même soin et la même précision qui doivent présider à l'usage d'agents puissants, il lui revient sans doute une place en clinique comme les autres vapeurs anesthésiques halogénées d'ailleurs.

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THE EFFECT OF INHALING DILUTE NITROUS OXIDE UPON RECENT MEMORY AND TIME ESTIMATION

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The stage of analgesia with amnesia which occurs with the inhalation of anaesthetic agents was recognized very soon after the introduction of ether. John Snow (1) described analgesia as the second degree of narcotism in which the pain of surgical operations was usually not felt. If there were responses to painful stimuli, they were either not remembered or recollected as having occurred in a dream. It is also of interest to note that he did not think it was necessary to maintain deeper anaesthesia for the greater part of protracted operations.

The recent work of Summerfield and Steinberg (2) has made it clear that relatively small quantities of nitrous oxide in the inspired air can interfere with the establishment of new memories. By testing the ability of human subjects to learn nonsense syllables, they have demonstrated that inhalation of a mixture of 30 per cent nitrous oxide in oxygen retards the learning process; at the same time, the presence of the anaesthetic appears to lock previous memory traces into the nervous system so that information acquired prior to the administration of nitrous oxide is forgotten less rapidly that it is by subjects breathing air.

We undertook our own experiments upon the effects of light nitrous oxide anaesthesia for two reasons, the one academic and the other practical. In the first place, it seemed that an investigation of any controllable procedure that interfered with learning might ultimately reveal something of the nature of learning mechanisms at the cellular level. Secondly, the current practice of combining light general anaesthesia with muscular relaxants has raised the question—how light should the anaesthetic be? It seems clear that the only requirement from the patient's point of view is that anaesthesia should be sufficient to produce amnesia for the period of operation. Artusio (3) has described the stage of amnesia produced by the inhalation of diethyl ether and its use in major cardiac surgery.

Our first attempts to investigate the influence of N_2O on the learning process were made in 1956. We were, therefore, unaware of the work of Summerfield and Steinberg (2) which was published in 1957. In this publication they showed clearly that the effect of N_2O on subjects learning nonsense syllables was to decrease the rate and to increase the retention of learning. These observations were entirely consistent with our own preliminary findings and we therefore turned our attention to other effects of N_2O inhalation. Thus the majority of the experimental results reported below describe a disturbance induced by nitrous oxide in estimates of the passage of time by human subjects and cats. Nevertheless those few

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experiments concerned with amnesia that we had completed are included in this report.

Methods

The Administration of Nitrous Oxide

Nitrous oxide and oxygen were administered from a standard Boyle's anaesthetic machine. A non-rebreathing system was provided by means of a Stephen-Slater valve placed close to a standard rubber face-piece. This face-piece contained a small microphone (unless a microphone, amplifier, and loudspeaker were used, it was difficult to understand the subject's speech).

Subjects

Twelve subjects were used for the experiments described in this and the succeeding (4) paper. There were two female subjects, and the ages of all subjects lay between 27 and 44 years.

Estimation of Time by Cats

A gas-tight box 12 in. high, 30 in. long and 12 in. wide was constructed; one wall of this box was transparent. The inner floor on which the cat walked was made of parallel brass strips of 1/8 in. separated by 1/8 in. spaces. A control unit was constructed to supply either half of the floor with sinusoidal 60 c.p.s. voltage between alternate metal strips; the current drawn by the cat could be measured and was approximately the same for all tests. The current used for these tests was sufficient to make the animals seek the unelectrified half of the floor, but was not enough to stop the cat purring.

The cats were trained to cross the midline of the box any time between the fifteenth and thirtieth second measured from the time at which they last crossed. If they tried to cross too early they encountered an electrified floor; if they stayed on one side for too long that side was electrified. The animals chosen for training were young cats of about 1 kg. Training was continued until they would cross the midline ten to fifteen times consecutively without error. Thus the experiments, the results of which are illustrated in Table III, were performed with cats crossing voluntarily and without any reinforcement. The required gas mixtures were supplied to the box through a half-inch pipe let into the floor. Before each exposure of the cat the box was flushed for 10 min. with the required gas mixture flowing at 10 L./min.

Results

Effects of Light Anaesthesia upon Recent Memory in Human Subjects

The Effects of 20–45 per cent nitrous oxide in oxygen. We have found considerable variation in the susceptibility of human subjects to nitrous oxide. While some subjects were invariably unreactive to all normal stimuli when exposed to 35 per cent N_2O, others were still talkative under 40 per cent and did not lose contact with their environment until there was 45 per cent N_2O in the inspired gas. Moreover, individual subjects vary in their susceptibility from day to day in a manner which apparently depends upon whether they feel sleepy or alert. These

facts make it difficult to define a concentration of nitrous oxide at which the amnesic effects that can be revealed by our tests are easy to demonstrate. In general, we have been able to record impaired memory for recent information when the subject is breathing a concentration of N_2O some 5 to 10 per cent lower than the critical concentration required to "put him to sleep."

Our procedure in these memory tests has been as follows. While breathing mixtures of nitrous oxide in oxygen the subject was shown a number clearly written on a card. The number, chosen at random from the series 1–12 was shown to the subject for 2 sec., and an indication that the number had been recognized was obtained. At 1/2, 2, and 5 min. after exposure of each new figure, the subject was handed a piece of paper and asked to record (*a*) the number that he was last shown, (*b*) all numbers that he had been shown in their correct order, (*c*) all numerals from one to ten, in order to test his ability to write. The inspired anaesthetic concentration was increased in steps and after 5 min. of exposure to each new concentration the number was presented and the subject's memory tested. Thus, because it takes at least 5 min. for cerebral equilibration with a new N_2O mixture (5) consecutive tests of recall were necessarily separated by about 10 min.

It was apparent that there is a concentration of nitrous oxide in the inspired gas which does not prevent the subject from writing normally or from conversing intelligently with those conducting the experiment, but which does prevent him from retaining new information, of the sort that we offered, for more than 1 or 2 min. Information which could not be recalled while under the anaesthetic could also not be recalled after the subject was returned to breathing pure oxygen. Tables I and II show the results of such experiments. As a control for the experiment of Table II we have exposed the same subject when breathing air to a similar set of numbers shown under identical conditions and no errors or omissions were made.

It is worth pointing out that the errors of recall illustrated in these tables are not random. Subjects always exhibited a tendency to return to the last number that had been recalled for 5 min. Thus, in Table II under 40 per cent N_2O, the

TABLE I

EFFECT OF VARIOUS CONCENTRATIONS OF N_2O ON MEMORY AND TIME ESTIMATION IN SUBJECT 2

Percentage of N_2O in O_2 in order used	Numeral shown	Response of subject* after 0.5	2 (min.)	5	Estimate of 15 sec. (sec.)
10	2	2	2	2	27
20	6	6	6	6	29
25	1	1	1	1	30
30	8	8	8	8	40
35	3	3	3	3	35.5
37	4	4	4	4	45
42	5	5	(4)	(4)	∞
42	7	(4)	(—)	(—)	∞
42	9	9	9	(—)	∞
37	10	(—)	(4)	(4)	—
35	12	12	12	(10)	—

*All errors and omissions are in parentheses

TABLE II

EFFECT OF VARIOUS N_2O CONCENTRATION ON MEMORY AND TIME ESTIMATION IN SUBJECT 5

Percentage of N_2O in O_2	Numeral shown	Response of subject* after 0.5 (min.)	2 (min.)	5 (min.)	Memory of series at fifth minute	Mean estimate of 15 sec. (sec.)
0	—	—	—	—	—	18.1
10	3	3	3	3	3	19.7
20	8	8	8	8	3 8	19.9
30	5	5	5	5	3 8 5	21.6
35	2	2	2	2	3 (5) (8) 2	23.4
40	6	6	(2)	(2)	3 (5) (8) 2 (—)	25.4
43	7	7	(2)	(2)	3 (5) (8) 2 (—) (—)	27.5
0	—	—	—	—	3 (5) (8) 2 (—) (—)	18.4

*All errors and omissions are in parentheses.

number 6 was retained for 1/2 min., but 2 min. after exposure the subject's response reverted to the number 2 exhibited under 35 per cent N_2O. The same tendency is displayed in Table I.

Note on the effects of diethyl ether. The clear-cut effect of N_2O upon learning demonstrated by Summerfield and Steinberg (2) and reported above, could be a specific property of N_2O or a property of all anaesthetic drugs. In our only experiment with diethyl ether, the subject of Table II exhibited a similar defect of learning. When his arterial blood contained 31.5 mg. of diethyl ether per 100 ml., his performance was equivalent to that when inhaling 40 per cent N_2O.

In this experiment the concentration of ether in the blood was progressively raised to 36.4 mg./100 ml. The subject had no recollection of any part of the experiment after the blood concentration reached 30 mg./100 ml., a period of 21 min. Despite this amnesia for recent events, the subject was capable during this time of directing the correct control of the anaesthetic apparatus and other prearranged experimental plans.

Notes on the general performance of subjects inhaling N_2O. Subjects inhaling a concentration of N_2O sufficient to prevent the recall of numbers which they had seen more than 1 min. earlier were able to write normally and able to converse "intelligently" with personnel conducting the experiment. Subjects who had recently learned English were still able to think and converse in this language. This sort of casual observation revealed no behavioural abnormalities. Nevertheless, abnormalities of behaviour can be revealed in subjects breathing 30 per cent N_2O (by psychological tests (6)). We were able, with the help of Dr. Brenda Milner (Clinical Psychologist, Montreal Neurological Institute), to expose some of our subjects while breathing N_2O to a few psychological tests which are listed in Table III. This table shows a comparison of the performance of the same subject when breathing air and when inhaling 40 per cent N_2O in oxygen. The figures of efficiency listed provide the ratio of the subject's score while under 40 per cent N_2O to his performance in air.

The subject of Table III proved quite incapable of performing the Wisconsin Card sorting test while under anaesthetic, although his scores were normal when he was breathing air.

TABLE III

Tests	Efficiency
Wechsler Intelligence	
Digit span	0.69
Mental arithmetic	0.50
Block design	0.57
Digit symbols	0.62
Wechsler Memory	
Immediate story recall	0.55
Visual recall	0.57
Paired associates	0.80

Effects of Nitrous Oxide on the Apparent Passage of Time

Human subjects. One of the notable features of light nitrous oxide anaesthesia is a disturbance in the subject's sense of the passage of time. The duration of the experiment invariably appeared to the subjects to be much shorter than was actually the case. Comments by the subjects in our early experiments led us to attempt a numerical estimate of the subjective passage of time.

Subjects were asked to tap an electrical key repeatedly once every 15 sec., during a control period while breathing oxygen, during the inhalation of a nitrous

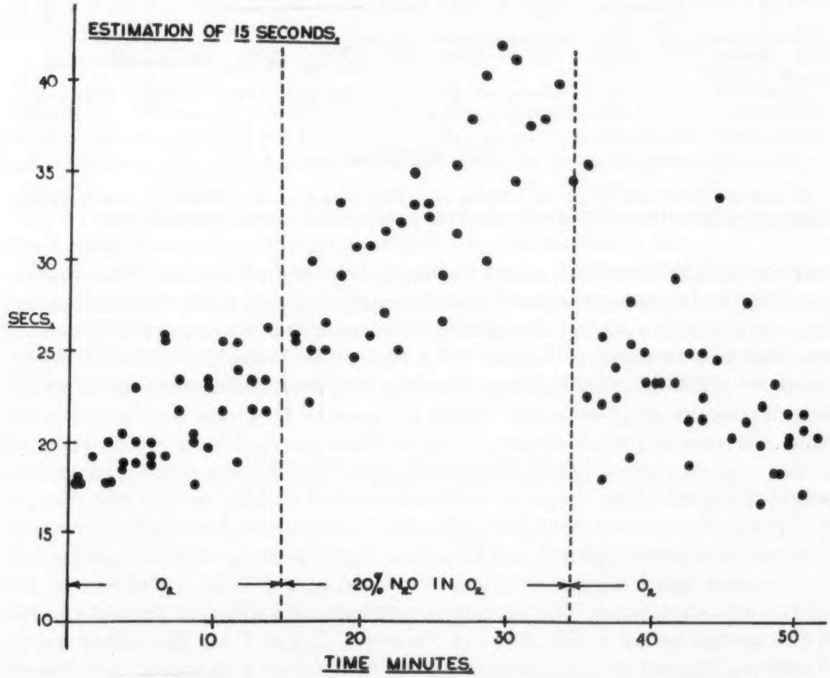

FIGURE 1. Estimates of 15 sec. during a control period of O_2 inhalation, during 20 min. inhalation of 20 per cent N_2O in O_2 and during a final control period. Subject 2.

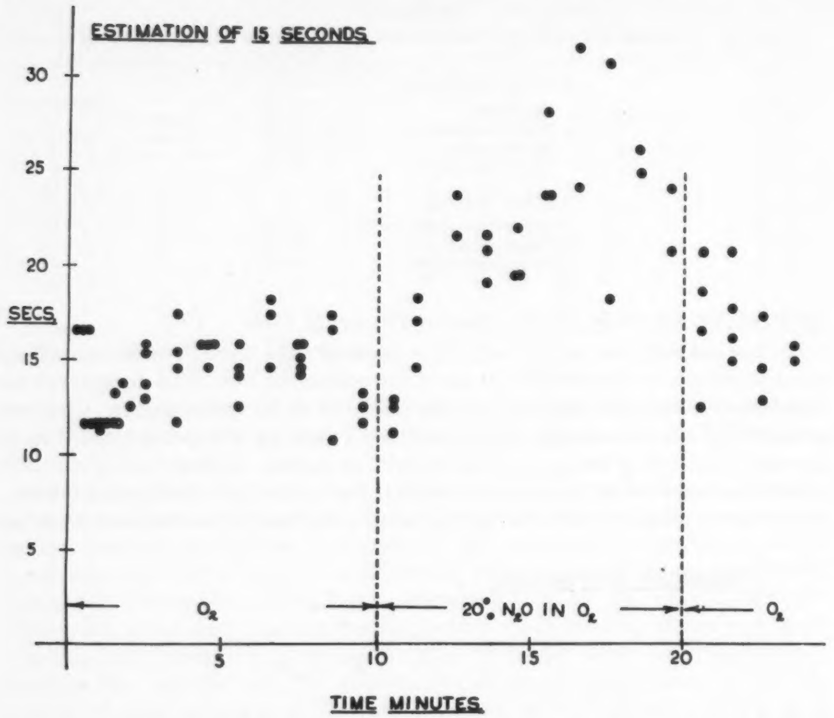

FIGURE 2. Estimates of 15 sec. during a control period of O_2 inhalation, during 10 min. inhalation of 20 per cent N_2O in O_2 and during a final control period. Subject 5.

oxide–oxygen mixture and again during a final control period. The contacts made by the key were registered on continuously moving paper. No communication was made with subject throughout the test and disturbance in the laboratory was kept to a minumum. Figures 1, 2, and 3 show the results of typical experiments on three different subjects. Directly subjects inhaled the nitrous oxide–oxygen mixture their estimates began to increase to a new and longer mean value. On returning these subjects to oxygen their time estimates rapidly reverted to the original control levels. During the first 15 min., the whole first control period of Figure 1, the subject's estimates climbed steadily so that the effect of N_2O inhalation was not clear until the subject was returned to breathing oxygen. The results of both Figures 1 and 2 indicate that the change from breathing N_2O to breathing pure oxygen produces a comparatively rapid reduction in the subject's time estimates. The increase of time estimations during the first minutes of the control period which shows in Figures 1, 2, and 3 has been observed by Waksburg (7), and this phenomenon forced us to adopt a prolonged first control period of about half an hour as is shown in the experiment of Figure 3. Figure 3, in addition to showing the effects of nitrous oxide, demonstrates the consequences of sensory disturbance. An abrupt fall in time estimates occurred when the

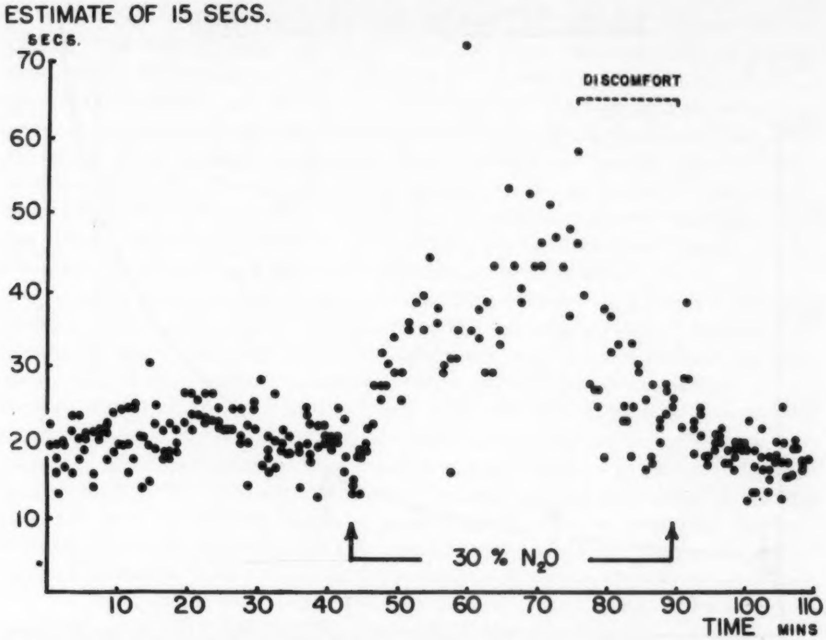

FIGURE 3. Estimates of 15 sec. during a control period of O_2 inhalation during 47 min. inhalation of 30 per cent N_2O in O_2 and during a final control period. Towards the end of the period of N_2O administration the subject complained of discomfort due to the face-piece. Subject 5.

subject began to complain of discomfort from pressure of the anaesthetic mask, which made us terminate the administration of nitrous oxide.

The distortion of time estimate produced by nitrous oxide was dependent upon the concentration inhaled. Figure 4 shows a curve relating mean time estimates to anaesthetic concentration for subject 2 (of Fig. 1).

Time estimation by cats. Young cats were trained by mild punishment (see Methods) to estimate time intervals within the range 15–30 sec. Table IV shows

TABLE IV
EFFECTS OF N_2O ON CAT'S TIME SENSE

Time tested (hrs.)	Breathing	Mean crossing time (sec.)	S.E.	p
1439–1446	Oxygen	18.5	±2.4	$\ll 0.01$
1514–1532	35% N_2O + 65% O_2	54.2	±7.0	—
1557–1611	Oxygen	38.9	±5.6	0.1
1636–1643	Oxygen	19.7	±2.3	$\ll 0.01$

NOTE: This cat was trained in air to cross the barrier between the fifteenth and the thirtieth second. The standard error of the mean crossing times is provided in column four. The fifth column gives the probability that the differences in mean crossing times from those observed under N_2O could have arisen by chance.

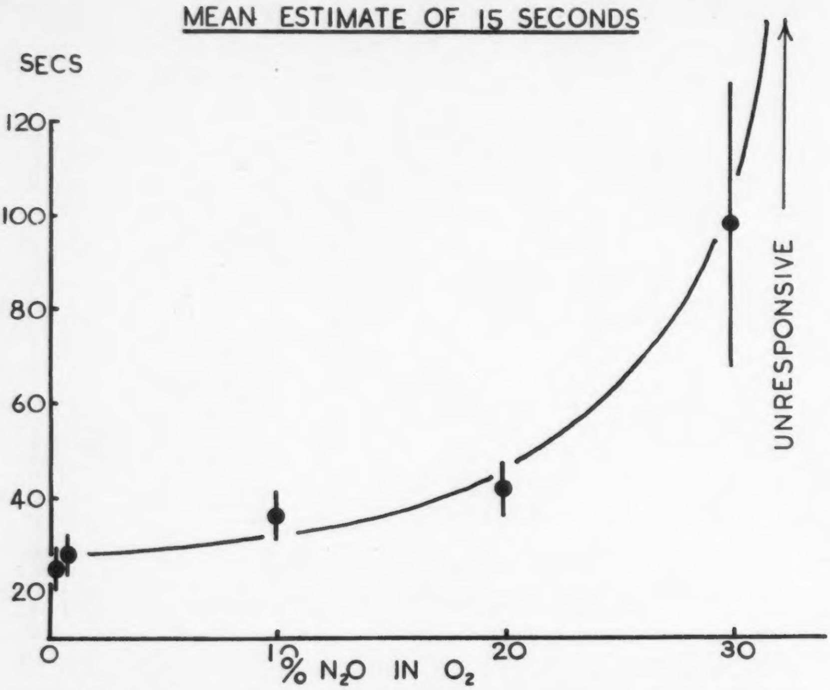

FIGURE 4. The relation between mean estimates of 15 sec. and concentration of inhaled N_2O in O_2 obtained in one experiment with Subject 2, exposed successively to 0, 20, 30, 10, 25, 0 per cent N_2O in O_2. The mean time estimates are plotted together with their standard errors. Each mean was determined in the last 5 min. of a 15 min period at each concentration of N_2O tested.

the performance of one cat during an initial control period, breathing oxygen, a period of breathing 35 per cent N_2O/O_2 and two final control periods on oxygen. These tests were run consecutively with no periods of retraining between tests. Thus, during the tests the animals received no electric shocks. This way of testing is essential in order to eliminate possible effects of nitrous oxide on the animal's threshold for electrical excitation. The animal's mean estimate of time was increased approximately threefold by the administration of nitrous oxide. It will be seen that recovery was not complete 25 min. after exposure to nitrous oxide; this finding is very different from our observations on humans who recover comparatively rapidly.

On casual inspection, cats breathing 35 per cent N_2O/O_2 showed no other deviations from normal behaviour. They walked normally and moved with normal speed; they would purr and play.

DISCUSSION

The work of Summerfield and Steinberg (2), taken together with the few results that we have reported above, makes it clear that the inhalation of 30–40 per

cent of nitrous oxide in oxygen interferes with the learning of meaningless material. This finding need not imply that the same concentration of nitrous oxide would produce amnesia for all sorts of sensory experience; nor need it imply that the production of amnesia is a property of all general anaesthetics. Nevertheless, Artusio (3) has demonstrated amnesia under light ether administration. Moreover, it is well known that ethyl alcohol has similar effects. These points seem to be of sufficient practical importance to merit further investigation. It would be useful to know the lower limits of anaesthetic concentration at which those sensory experiences likely to occur during surgical operation would not be remembered; this has been done for diethyl ether by Artusio (3).

The study of any controllable procedure which interferes with learning is likely to produce information about the nature of the learning process. There is considerable evidence that both concussion and electroshock are accompanied by a variable period of retrograde amnesia. Trotter (8) defined concussion as ". . . a transient state due to head injury which is of instantaneous onset, manifests widespread symptoms of a purely paralytic kind, does not as such comprise any evidence of structural cerebral injury and is always followed by amnesia for the actual moment of the incident." The extent of memory defects following cranial injury has been studied by Williams and Zangwill (9) who employed psychological tests. It is generally agreed that electroshock in humans causes a variable retrograde amnesia. Janis (10) studied the nature and extent of amnesia produced by E.C.T. and commented that although amnesia was "spotty" the subjects usually exhibited most difficulty in the recall of recent events.

There is an unfortunate absence of quantitative information concerning the amnesia produced by electroshock in humans (but see Kronholm and Molander (11)). On the other hand, the results of experiments in which rats received electroshock (12, 13) have shown shock to be associated with a retrograde amnesia of some 20 min. duration. Burns (14) has pointed out that there may be a mechanism common to the events of concussion and electroshock; there is evidence that a form of Leao's (15) spreading cortical depression accompanies both conditions.

The information available about concussion and electroshock tells us little about those neurophysiological changes which accompany memory formation, but indicates that these changes, whatever their nature, are peculiarly vulnerable soon after they have occurred.

At first sight there are two possible interpretations which might be made of the observed effects of N_2O on the learning of meaningless material. One could assume that those changes produced in the central nervous system by recent learning decayed more rapidly in the presence of N_2O than they do in subjects breathing air. This interpretation would make the effects of N_2O on the central nervous system appear similar to those of concussion and electroshock. However, this assumption is not consistent with all of the available facts. Summerfield and Steinberg (2) have shown that N_2O not only reduces the rate of learning but also retards the rate of forgetting. They have pointed out that this unusual persistence of previous memories may itself be responsible for the decreased rate of learning in subjects breathing N_2O. Our own results illustrated in Tables I and II are entirely consistent with this view; in the fifth line of Table II, when the subject was expected to recall the figure "6" after 2 min., he not only failed to

recall the correct numeral but offered with confidence the numeral "2." It would be easy to interpret this observation by assuming that an abnormally persistent response of the subject to the number "2" prevented the following numbers from being learned.

One of the most remarkable effects of N_2O is the disturbance it produces in the subject's ability to estimate correctly the passage of time. The curve of Figure 4 suggests that one might usefully define "consciousness" as the reciprocal of the subjective time estimate. Whatever the mechanism by which human subjects assess the passage of time it is clear that memory forms an essential element. Unfortunately, we do not know whether amnesia, however produced, is invariably associated with disturbances in time sense. This problem would be well worth investigation; that such an investigation might prove profitable is suggested by the observation of Williams (16) who investigated patients with Korsakow's syndrome and subjects exposed to E.C.T. and concluded that "localization in time and the recall of serial order of recent events are aspects of memory particularly liable to dissolution in organic amnesic states." In the case of N_2O we have an empirical correlation between amnesia for number and disturbance of time judgment. The fact that dilute N_2O produces the same disturbance of time judgment in cats as it does in humans suggests that the action of the drug is similar in both species. This is a point of some technical importance because it provides another procedure which is known to interfere with the learning process and which can therefore be used to test potential learning mechanisms at the cellular level in experimental animals. For example, the synaptic facilitation proposed by Eccles and MacIntyre (17) as a hypothetical mechanism of learning could readily be tested for its susceptibility to N_2O.

We have not here attempted any discussion of possible mechanisms of time judgment. This problem is considered in another publication (4) where the effects of N_2O upon sensory thresholds are reported.

Summary

1. Human subjects and cats breathing a weak mixture of nitrous oxide (10–40 per cent) in oxygen have been observed.

2. Human subjects breathing 30–40 per cent N_2O are not able to retain and recall new information for a period exceeding 2 or 3 min.

3. Both human subjects and cats when breathing 10–40 per cent N_2O estimate time as passing more slowly than do the same subjects breathing oxygen or air.

4. In human subjects, deviation from normal time sense increases with increasing dose of anaesthetic.

Acknowledgment

Part of this work was supported by funds allocated to one of us (B. D. B.) by the National Research Council of Canada, to whom we would like to express our thanks.

RÉSUMÉ

Dans un travail récent, Summerfield and Steinberg (2) nous ont démontré clairement que des quantités relativement petites de protoxide d'azote dans l'air inspiré pouvaient nuire à l'établissement du souvenir de choses nouvelles. L'inhalation d'un mélange de 30% de protoxide d'azote dans de l'oxygène retarde ou diminue la capacité d'apprendre mais elle semble aussi réduire la vitesse d'oublier. Les expériences décrites dans ce travail et dans le suivant sont un sondage pour essayer de trouver comment le protoxide pourrait produire ces effets. Cela présente un grand intérêt et pour les anesthésistes qui, de plus en plus, emploient des plans d'amnésie en clinique et pour les physiologistes parce que tout procédé contrôlable qui pourrait nuire à la faculté d'apprendre pourrait bien, en définitive, apporter des renseignements sur le mécanisme de la capacité d'apprendre au niveau cellulaire. La plupart des résultats d'éxperiences que l'on donne plus loin illustrent un dérangement occasionné ou produit par l'inhalation de protoxide d'azote par des humains ou des chats des évaluations de périodes de temps qui s'écoulent.

Les tableaux 1 et 2 montrent les effets de diverses concentrations de protoxide d'azote sur la capacité de se souvenir de chiffres et confirment, de façon simple, le travail de Summerfield et de Steinberg. Le tableau 3 donne une vue d'ensemble de l'impuissance à subir les tests ordinaires d'intelligence chez un sujet qui respire 40% de protoxide d'azote dans de l'oxygène. Le tableau 4 montre l'effet que produit le protoxide d'azote sur l'aptitude à mesurer une période de temps chez un chat entraîné. Les schémas de 1 à 3 montrent les effets de l'inhalation de protoxide d'azote, chez trois sujets, sur l'évaluation de périodes de 15 secondes; le schéma 4 montre la relation entre diverses concentrations inhalées de protoxide d'azote et les évaluations de périodes de 15 secondes.

La courbe du schéma 4 suggère que l'on pourrait, à toute fin pratique, définir l'état de conscience comme la réciproque de l'évaluation subjective du temps qui passe. Peu importe le mécanisme par lequel les humains évaluent le temps qui passe, il est manifeste que la mémoire joue un rôle essentiel. En employant le protoxide d'azote, nous établissons une corrélation empirique entre l'amnésie de chiffres et la perturbation dans l'évaluation d'une période de temps. Le fait que le protoxide d'azote produit les mêmes perturbations chez le chat et chez l'homme en ce qui concerne l'évaluation de périodes de temps, ce fait laisse croire que l'action du médicament est la même chez les deux espèces. Les mécanisme probables de l'évaluation du temps qui passe font l'objet du travail suivant.

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THE EFFECTS OF NITROUS OXIDE UPON SENSORY THRESHOLDS

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IN THE PRECEDING PAPER (1), we have shown that nitrous oxide distorts the subjective passage of time in human subjects and in cats. Subjects breathing 20 per cent N_2O in oxygen provided estimates of 15 sec. periods approximately twice as great as those they provided when breathing air. This observation made us interested in the physiological mechanism responsible for the subjective estimation of 15 sec. periods.

There is a large literature on subjective time estimation (2) and various possible mechanisms have been proposed. For instance, Hoagland (3) suggested that estimates of the passage of time were dependent upon the speed of the slowest of a series of chemical reactions underlying neurophysiological events. He was able to show that subjective estimates of time changed with change of body temperature.

It is impossible in the present state of neurophysiological knowledge to specify the neural events responsible for time estimation. One could, for instance, postulate that estimation of time depends upon the rate of decay of some relatively enduring central change which is maximal at time zero. Thus, if the instruction "estimate 15 seconds from now," caused some change in the central nervous system which decayed progressively with the passage of time, one might suppose that the response of the subject was triggered when the initial change had decayed to a particular and learned value. Our results (1) might therefore be explained by assuming that nitrous oxide reduces the speed of decay. There is some evidence that changes produced in the central nervous systems of subjects breathing nitrous oxide decay less rapidly than usual. Thus Summerfield and Steinberg (4) have shown that human subjects who have learned nonsense syllables forget them less rapidly when breathing nitrous oxide than they do when breathing air.

Alternatively, the subjective estimation of time might depend upon an integration of a number of remembered events. Thus a subject asked to estimate a 15 sec. interval would complete this period when a learned number of remembered sensory events had accumulated. In support of this hypothesis is the accepted view that time appears to pass more rapidly for subjects in changing environments (2, 5). This concept of time estimation would imply that nitrous oxide produces an increase in subjective time estimates by affecting a reduction in the rate of accumulation of new, remembered events. Summerfield and Steinberg have, in fact, also shown that the number of nonsense syllables which can be learned in unit time is reduced by inhalation of nitrous oxide. This effect of

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nitrous oxide in reducing the number of enduring responses to a series of standard external stimuli might be due to one of two mechanisms. There is evidence that nitrous oxide locks recently learned events into the central nervous system (4); thus, we could suppose that new information was hard to acquire in the presence of nitrous oxide because it was in competition with old information for the same storage mechanism. That such competition for the storage mechanism can occur in normal circumstances is well established (6). Alternatively one might suppose that the main effect of nitrous oxide was to interrupt some part of the pathways from sensory endings to the storage mechanism and so reduce the information available for storage. The production of analgesia by nitrous oxide provides an example of such an effect. Although the action of nitrous oxide upon response to pain is well established, little information is available about the effect of light general anaesthesia on other sensory modalities (7, 8).

For these reasons we have tested the effect of nitrous oxide upon a variety of sensory thresholds.

Method

Subjects

Twelve subjects were used for the experiments described in this and the preceding paper (1). There were two female subjects and the ages of all subjects lay between 27 and 44 years.

Apparatus

Estimation of threshold for skin pain. For this experiment 10 cm. of 0.2 mm. diameter platinum wire were wound around a U-shaped glass tube of 3.5 mm. external diameter, so that only one turn of this wire made contact with the skin when the instrument was pressed upon the forearm. The wire was heated by current supplies from an A.C. source variable between zero and 6.3 volts. Thresholds were recorded in terms of voltage.

Estimation of warmth thresholds. Radiant heat was supplied from a 250-watt General Electric heat lamp supported 18 in. above the subject's hand. The current through the lamp was controlled by a "Variac" mains transformer. A cardboard screen with an aperture was clamped between the lamp and the subject's hand and restricted the radiation to a circular area of 1 in. in diameter. The stimulus was interrupted for 1 sec. in 2 sec. by closing the aperture. Thresholds were recorded as volts supplied to the filament.

Estimation of touch threshold. A hollow solenoid was constructed by winding 140 turns of 0.31 mm. varnished copper wire onto a plastic bobbin 13 mm. long with a central hole of 5.0 mm. diameter. The mobile core was made by gluing 1 cm. of soft iron rod to an equal length of glass rod 2.3 mm. in diameter; the core was a loose fit to the bore of the bobbin. The instrument was applied to the skin with the axis of the bobbin in the vertical plane; the core was dropped into place so that the glass rested upon the skin. Current pulses of 1 sec. in 2 sec. were supplied to the coil, the resultant thrust of the core deforming the skin. Thresholds were recorded as volts applied to the coil.

Estimation of thresholds of brightness discrimination. The durations of the flashes of light from the neon bulb used to determine the thresholds of brightness discrimination were controlled by means of a Tektronix pulse generator no. 161. Details of the procedure which we used are given in the text.

Estimation of thresholds of hearing. The output of a variable frequency sinusoidal oscillator (Krohn-Hite no. 420-A) was fed through an attenuator to a pair of rubber-cuffed earphones. Thresholds were recorded as volts supplied to the earphones.

RESULTS

Effects of nitrous oxide on human sensory threshold

Skin pain. The elevation of threshold for skin pain by light general anaesthesia is well known (7). In our own experiments 20 per cent of nitrous oxide abolished the sensation of pain accompanying a pin prick sufficient to draw blood.

In order to have a more sensitive measure of pain threshold we used an electrically heated wire in contact with the skin. In any series of consecutive tests the wire was pressed onto the skin by the subject with sufficient pressure to cause blanching and held there until the steadily rising temperature became intolerable. The thresholds obtained in these experiments were expressed in terms of that voltage which, when applied to the heating element, forced the subject to remove the wire. The voltage applied to the wire was increased at a slow and constant rate. After each threshold estimation a neighbouring piece of skin was used for the next trial. Some of the results are provided in Table I.

TABLE I

SKIN PAIN THRESHOLDS (WATTS)

Subject	Control (breathing air)	25% N_2O in O_2	Ratio of mean thresholds	p
1	27.6±1.4 (6)	47.6±3.2 (6)	1.72	<.0005
2	23.1±1.1 (6)	45.3±1.2 (6)	1.96	<.0005
3	17.7±2.3 (6)	28.3±2.2 (6)	1.60	.005 –.0005
4	34.1±2.8 (6)	51.2±3.6 (5)	1.50	.005 –.0005

Columns 2 and 3 provide the mean thresholds ± their standard errors, with the number of observations in brackets. The fifth column provides the probability that a difference between the means, as great or greater than that found, could be due to chance.

Warmth threshold. Radiant heat was supplied from a filament-bulb to a circular area of skin, 1 in. in diameter, on the back of the hand. The stimulus was interrupted so that heat was supplied for 1 sec. in 2 sec. The distance between the heat source and the hand was kept constant and the subject was unable to see any light from the lamp. The threshold for the first perception of warmth was obtained by slowly increasing the voltage applied to the filament. Thresholds were also obtained for the disappearance of perceptible warmth as the temperature of the source was reduced from a value providing an unquestionable sensation. In preliminary experiments we found, as might be expected, that the thresholds

measured in this way were very dependent upon skin blood flow. For this reason all the thresholds that are reported below were recorded while blood flow to the forearm was temporarily arrested with a sphygmomanometer cuff. The results are reported in Table II.

TABLE II

WARMTH THRESHOLDS (WATTS)

Subject	Change in test temperature	Control (breathing air)	25% N_2O in O_2	Ratio of mean thresholds	p
1	Increasing	36.5±1.2 (6)	52.4±3.1 (6)	1.44	<.0005
	Decreasing	36.9±2.2 (6)	35.4±4.8 (6)	.96	.3–.35
2	Increasing	41.6± .8 (6)	118.2±1.4 (6)	2.84	<.0005
	Decreasing	50.1±3.1 (6)	130.3±2.2 (6)	2.60	<.0005
3	Increasing	47.8±1.0 (6)	100.9±3.5 (6)	2.10	<.0005

Columns 3 and 4 provide the mean threshold ± their standard errors with the number of observations in brackets; p is entered as in Table I.

Touch threshold. Touch thresholds were measured on the lateral surface of the pulp of the little finger. Since the deformation of the skin was produced electromagnetically, thresholds for touch were measured in volts applied to the solenoid, which was energized for about 0.1 sec. at regular intervals (once in 2 sec.); an audible click occurred with each pulse. The instrument was calibrated in terms of weight applied to the skin. Subjects were asked to identify the thresholds for touch with both increasing and decreasing voltages applied to the coil. The results are summarized below in Table III.

TABLE III

TOUCH THRESHOLDS (GM.)

Subject	Change in stimulus strength	Control (breathing air)	25% N_2O in O_2	Ratio of mean thresholds	p
1	Increasing	0.70±.02 (6)	3.20±.15 (6)	4.57	<.0005
	Decreasing	0.54±.17 (6)	2.75±.06 (6)	5.09	<.0005
2	Increasing	1.21±.06 (6)	1.63±.08 (6)	1.35	.0005–0.005
	Decreasing	0.01±.05 (6)	1.45±.08 (6)	1.44	<.0005
4	Increasing	0.66±.06 (6)	1.14±.21 (6)	1.73	.025–.05
	Decreasing	0.69±.04 (6)	1.06±.17 (6)	1.54	.025–.05

Columns 3 and 4 provide the mean thresholds ± their standard errors with the numbers of observations in brackets; p is entered as in Table I.

Thresholds for brightness discrimination. The subjects were asked to observe, from a fixed distance, an opaque, white screen which had a constant surface-illumination. In the centre of this screen was a circular, translucent area, 1 in. in diameter, which could be illuminated from behind; when illuminated only from the front, it appeared to be no different from the rest of the screen, but a small black spot was placed on it to allow fixation. The central translucent area could be made periodically brighter than the surround by the flashes of a neon

bulb behind the screen. The intensity of the neon flash was constant, while its duration was variable. Thresholds of brightness discrimination were therefore measured in milliseconds. The flashes were repeated once per 2 sec. and the duration of the flash was increased from zero until the translucent area was just perceptible. Measurements of threshold were also made by decreasing the flash duration from suprathreshold values. The results are summarized in Table IV.

It is interesting to note that the thresholds, as determined for one eye were almost twice that determined for two eyes.

TABLE IV

THRESHOLDS FOR BRIGHTNESS DISCRIMINATION (M.SEC.)

Subject	Using	Direction of change	Control (breathing air)	25% N_2O in O_2	Ratio of means	p
1	2 eyes	Increasing	17.8± .3 (6)	22.5±1.5 (6)	1.26	.005–.01
		Decreasing	15.4±1.1 (6)	19.7±1.4 (6)	1.28	.01–.025
	1 eye	Increasing	29.7±1.2 (3)	34.3± .7 (3)	1.15	.01–.025
		Decreasing	31.2±1.2 (3)	35.0±2.9 (3)	1.12	.01–.15
2	2 eyes	Increasing	16.0±1.1 (5)	28.5±1.0 (6)	1.78	<.0005
		Decreasing	16.2± .7 (6)	25.5± .6 (6)	1.57	<.0005
	1 eye	Increasing	30.0±1.5 (3)	46.3±2.0 (3)	1.54	<.0005
		Decreasing	30.6±2.7 (3)	46.6±3.5 (3)	1.52	.005–.01
4	2 eyes	Increasing	17.8±1.0 (6)	26.7±1.4 (6)	1.50	<.0005
		Decreasing	15.5±1.0 (6)	16.7±1.4 (6)	1.08	.3–.35
	1 eye	Increasing	27.3± .8 (3)	38.7±2.2 (3)	1.42	.005–.0005

Columns 4 and 5 provide the mean thresholds ± their standard errors with the number of observations in brackets; p is entered as in Table I.

Thresholds of hearing. The subjects of these tests wore earphones, through which they were presented with a 500 c.p.s. note of variable intensity. The threshold was measured as the voltage supplied to the earphones by the oscillator. Thresholds for both increasing and decreasing voltage were measured and the results appear in Table V.

TABLE V

THRESHOLDS OF HEARING
(WATTS $\times 10^{-9}$ SUPPLIED TO EARPHONES)

Subject	Changes in stimulus strength	Control (breathing air)	25% N_2O in O_2	Ratio of mean thresholds	p
1	Increasing	1.91± .26 (6)	13.72± 2.33 (6)	7.18	<.0005
	Decreasing	2.02± .24 (6)	8.70± .91 (6)	3.59	<.0005
2	Increasing	3.77± .43 (6)	82.48±14.92 (6)	21.90	<.0005
	Decreasing	6.74±1.46 (6)	73.10±12.20 (6)	10.85	<.0005
3	Increasing	.092± .026 (6)	4.33± .56 (6)	47.10	<.0005

NOTE: Columns 3 and 4 provide the mean thresholds ± their standard errors with the number of observations in brackets; p is entered as in Table I.

Effects on proprioception. We did not measure proprioceptive thresholds directly. The subject was asked to rest his arm and forearm horizontally upon a table and to flex and extend the elbow-joint, so that his hand travelled about 15 cm. across the table. A piece of paper was pinned to the table and the subject was instructed to move a pencil-tip between two pegs 15 cm. apart. The subject's eyes were shut during these tests. After three trials of moving between the two pegs, one peg was withdrawn; the subject was then instructed to move the pencil from the remaining peg to the estimated position of the peg which had been removed, and mark the paper. He performed this operation ten times while breathing air and ten times under 25 per cent N_2O.

We were primarily interested in assessing the subject's error of proprioceptive estimation. For each trial we determined the average position of his estimate of the target distance. His error was scored as the mean deviation of his ten individual estimates (in centimetres) from this average position. Thus the second and third columns of Table VI provide the mean deviation and its standard error for our various subjects. There is some evidence from the results listed in Table VI that 25 per cent N_2O produced a small increase in proprioceptive error; but for only one of our subjects was this increase statistically significant.

TABLE VI

ERRORS OF PROPRIOCEPTION (CM.)

Subject	Breathing air	25% N_2O in O_2	Ratio of mean errors	p
1	.81±.24 (10)	1.45±.31 (10)	1.79	.05 –.1
2	1.24±.24 (10)	.98±.35 (10)	.80	.25 –.3
3	.30±.06 (10)	.62±.16 (10)	2.07	.025–.05
4	2.36±.38 (10)	2.59±.48 (10)	1.10	.35 –.4

NOTE: For explanation of entries see text.

We assume that any changes in true proprioceptive threshold should bear a direct relation to the proprioceptive error we have defined above.

Summary of effect of 25 per cent N_2O in O_2 on sensory thresholds. The results given in the tables above enable one to make a crude comparison of the vulnerability of various sensory mechanisms to 25 per cent nitrous oxide. Any such comparison must be dependent upon the units which are chosen to represent the strengths of the various stimuli used.

We have measured auditory threshold in terms of watts supplied to the earphones worn by the subject. Warmth thresholds have been estimated in terms of watts consumed by the filament heating lamp. Pain thresholds were determined as that point at which a hot wire became intolerable and are given in terms of watts consumed by the wire. When measuring thresholds for brightness discrimination we varied the duration of a constant intensity source, thus our units (msec.) are proportional to quantity of light reaching the eye. Touch thresholds were estimated in grams weight distributed over a contact area of 8 $mm.^2$. Proprioceptive error was measured in terms of centimetres which are proportional to degrees of arc.

Table VII provides a comparison (taken from the data given in the other tables) of the effects of 25 per cent nitrous oxide in oxygen on the various sensory thresholds for one of our subjects.

TABLE VII

COMPARISON OF EFFECTS OF 25 PER CENT NITROUS OXIDE ON SENSORY THRESHOLDS IN ONE SUBJECT (NO. 2)

Sensation	Ratio of thresholds (mean threshold under N_2O mean threshold in air)	Units
Hearing	11 -22	Watts supplied to earphones
Warmth	2.6 -2.8	Watts through filament lamp
Skin pain	2.0	Watts through heating wire
Vision (two eyes)	1.6 -1.8	(Constant intensity) × (msec.)
Touch	1.35-1.44	gm./8 mm.[2]
Proprioception error	.80	Degrees of arc

NOTE: Time estimates for this subject under N_2O were 1.76× (estimates while breathing air).

Effects of Environment upon Subjective Time Estimation

In the introduction to this paper, we pointed out that one mechanism by which subjects may estimate short time intervals might depend upon an integration of sensory events recorded by the nervous system. This hypothesis implies that

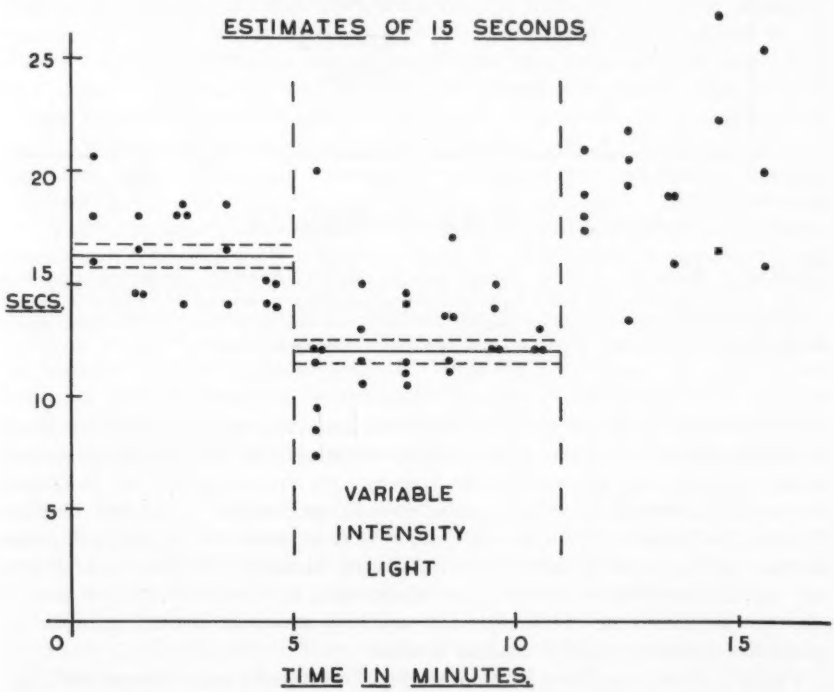

FIGURE 1. Estimates of 15 sec. periods made by Subject 5 in relative sensory isolation. First period, control in dark and silent room; second period, during illumination of room with light of randomly varied intensity; third period, control in darkness. The mean and its standard error are indicated during the first and second periods by continuous and dotted lines respectively.

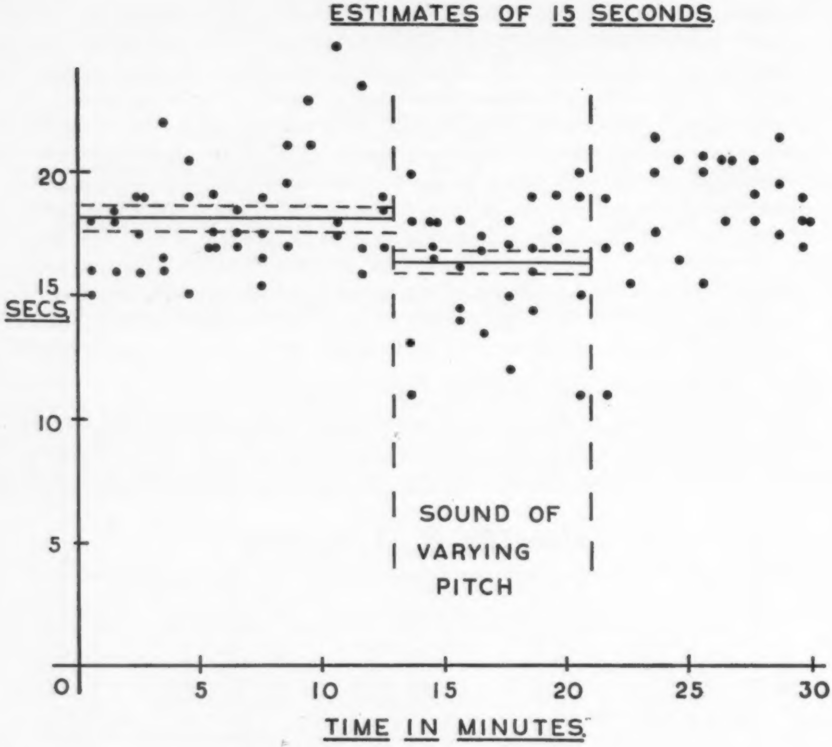

FIGURE 2. Estimates of 15 sec. periods made by Subject 1 in relative sensory isolation. First period, control in dark and silent room; second period, subject exposed to sound of randomly varied pitch; third period, control in silence. The mean and its standard error are indicated during the first and second periods by continuous and dotted lines respectively.

subjects breathing air should give subjective estimates of time which are longer in an environment of comparative sensory isolation than in a changing environment. There is some evidence in the literature that this is so (2). We attempted to test this prediction on subjects asked to make estimates of 15 sec. continuously (1) in a controlled environment. These subjects wore earphones and lay upon a bed in a quiet room which could be completely darkened. Thus we were able to test the effects of visual and auditory stimuli upon subjective estimation of time. Our results show that the addition of auditory or visual stimuli decrease the subjective estimation of the passage of time.

Figure 1 shows the effects of illuminating the subject's environment with light of an intensity which was varied at random with respect to time. Similarly Figure 2 shows the effect of providing sound, the intensity and frequency of which was randomly varied with respect to time.

Discussion

The purpose of the experiments that we have described was to test a specific hypothesis concerning the mechanism by which human subjects estimate short time intervals of the order of 15 sec. We gave our reasons in the introduction to this paper for suspecting that time intervals of this magnitude were determined by the amount of sensory information reaching the central nervous system in unit time. Thus we supposed that a subject asked to estimate a 15 sec. period would complete this period when an appropriate number of sensory events had accumulated. An analogous mechanism would be the performance of an electronic (or mechanical) digital scaling unit arranged to provide a signal when a pre-set count of ingoing information had been attained. In this situation any factor which would block every second signal at the input, would clearly cause an average delay of the output signal of 100 per cent. Fortunately it is possible to postulate and to test a series of supposed functions of the nervous system without specifying the precise neural mechanisms by which these functions are achieved. We believe that our results support this hypothesis.

The number of subjects examined in these experiments was very small. Nevertheless, they all showed significant increases in the majority of sensory thresholds that we tested. We have measured responses which are closely related to the sensory thresholds of hearing, warmth, superficial pain, brightness discrimination, touch and proprioception. The inhalation of 25 per cent nitrous oxide appears to raise the threshold for all these modalities of sensation except proprioception. Even in the case of proprioception most of our subjects showed an elevation of threshold, but this was only statistically significant in one subject. The comparatively small effect of nitrous oxide upon proprioception is surprising because all our subjects mentioned a feeling of dizziness. Despite this subjective sensation which made the subjects unwilling to stand up, it was in fact possible for our subjects to stand unsupported and to walk along a straight line. We are unable to account for the discrepancy between subjective sensation and the measurements of proprioception; it is possible that although 25 per cent nitrous oxide has little or no effect on proprioception, it has far more effect upon the central vestibular system. There are several modalities of sensation which we have made no effort to test, but our results make it clear that with 25 per cent N_2O in O_2 there must be a considerable reduction in the sensory inflow to the central nervous system.

The subjects of Tables I to VI were also asked to reproduce 15 sec. time intervals (1) and all subjects showed a prolongation of the subjective passage of time when equilibrated with 25 per cent nitrous oxide in oxygen. This increase of time estimate ranged from 20 to 80 per cent of their control values.

Our information, therefore, provides an empirical correlation between the distortion of the subjective time estimate produced by nitrous oxide and the simultaneous elevation of many sensory thresholds.

Our experiments with the effect of environment upon the subjective time estimation (p. 417) were undertaken in an attempt to reduce in a different way the amount of information available to the central nervous system. We only

varied the information presented to the auditory and visual systems, but our results showed clearly that subjective estimates of the passage of time were directly related to this variation. This finding is not surprising since it has often been assumed that "the experience of a certain duration is related to the total amount of experience (sensations, perceptions, cognitive and emotional processes, etc.) which takes place within this time period" (2).

We have suggested above that the human central nervous system estimates time intervals by an integration of experienced sensory events. An alternative mechanism for time estimation, as we have said in the introduction to this paper, might be dependent upon the slow decay of changes set up within the nervous system by the instruction. Thus one might postulate that when a subject is asked to estimate 15 sec. "beginning from now" the word "now" sets up instantaneously a change of state which decays slowly with time. When this trace has decayed to a learned fraction of its initial value the subject responds. Such a mechanism would not be inconsistent with the findings of Summerfield and Steinberg (4), who showed that subjects under 30 per cent N_2O learned less readily and forgot less rapidly than did the same subjects breathing air. They assume in their paper that the primary action of nitrous oxide is to stablize the memory trace, thereby making it more difficult for new information to compete for the storage mechanism. We know of no reason for rejecting such an explanation, but the results described in this paper make this hypothesis superfluous.

In our opinion the general increase in sensory thresholds which we have described for subjects breathing 25 per cent nitrous oxide provides a sufficient explanation of the three other important changes induced by this anaesthetic. The distortion of time sense, the increase in retention of previously acquired information and the decreased ability to accept for storage newly presented facts, could all be the consequence of the change in sensory thresholds.

Summary

1. Sensory thresholds have been measured in human subjects while breathing 25 per cent nitrous oxide in oxygen.

2. Nitrous oxide produced a significant and sometimes dramatic increase in the thresholds for touch, skin pain, warmth, vision, and hearing.

3. Elevations in proprioceptive thresholds were not significant.

4. It is suggested that the general increase in sensory thresholds produced by nitrous oxide is a sufficient explanation of the disturbances of memory and time sense that have been observed with nitrous oxide inhalation.

Acknowledgment

Part of this work was supported by funds allocated to one of us (B. D. B.) by the National Research Council of Canada, to whom we should like to express our thanks.

RÉSUMÉ

Dans une publication antérieure, nous avons démontré que des sujets respirant un mélange de 20% de protoxide d'azote et d'oxygène faisaient des évaluations de périodes de 15 secondes environ deux fois plus longues que celles qu'ils ne font lorsqu'ils respirent de l'air. On pourrait présumer que l'évaluation d'une période de temps dépend de la vitesse de décalage de certains changements centraux relativement difficiles à faire et qui sont à leur maximum lorsque la durée est brève. Alternativement, l'évaluation subjective d'une période de temps dépend de l'intégration d'un nombre d'événements dont on se souvient. Ainsi un individu à qui on demande d'évaluer ou de mesurer une période de 15 secondes ne pourra le faire seulement quand il aura accumulé un nombre connu d'événements sensoriels dont il se souvient. Le deuxième concept de l'évaluation d'une période de temps supposerait que le protoxide d'azote inhalé entraînerait une augmentation des évaluations subjectives des périodes de temps en produisant un ralentissement dans l'accumulation des événements dans la mémoire. Cela supposerait que le principal effet du protoxide d'azote inhalé serait d'interrompre une certaine partie des trajets nerveux à partir des terminaisons nerveuses jusqu'au mécanisme d'emmagasinage et aussi de réduire les renseignements disponibles pour l'emmagasinage. Bien que l'action du protoxide d'azote sur la réponse à la douleur soit bien connue, on possède peu de renseignements sur l'effet d'une anesthésie générale légère sur les autres modalités sensorielles. C'est pour ces raisons que nous avons étudié les effets de l'inhalation de protoxide d'azote sur un certain nombre d'autres seuils sensoriels.

Tous les sujets observés ont manifesté une augmentation évidente de la plupart des seuils sensoriels que nous avons étudiés. L'inhalation de 25% de protoxide d'azote semble élever le seuil pour toutes les modalités de sensations à l'exception de la proprioception. C'est ainsi qu'il existe une corrélation empirique entre la distorsion des estimations subjectives de périodes de temps par l'inhalation de protoxide d'azote et l'élévation simultanée de plusieurs seuils sensoriels. Nous avons modifié les renseignements offerts aux systèmes auditif et visuel chez des sujets qui n'étaient pas soumis à des inhalations de protoxide d'azote et les résultats démontrent clairement que les évaluations subjectives du temps qui passe étaient en rapport direct avec cette variation. Cela avait pour but d'essayer de réduire d'une autre façon la quantité de renseignements à la disposition du système nerveux central.

La perturbation du sens de la mesure du temps, l'augmentation de l'emmagasinage des renseignements acquis antérieurement et la diminution de l'aptitude à accepter pour emmagasinage des faits présentés récemment, choses qui surviennent chez ceux qui inhalent de faibles concentrations de protoxide d'azote, tout cela ne pourrait être que la conséquence d'un changement des seuils sensoriels.

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INDUCED SYMPATHETIC STIMULATION DURING HALOTHANE ANAESTHESIA

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GANGLIONIC BLOCKADE, at first considered to be the principal factor in the hypotensive action of halothane (12), was later shown to play only a subsidiary role; direct myocardial and vascular depression and central vasomotor inhibition were considered to be of greater importance (2, 3, 13). It has been suggested, however, that autonomic depression and even a protective action against shock are features of halothane anaesthesia (6, 7) although the mechanisms and evidence behind any such effects have not been defined.

Previous experiments in dogs lightly anaesthetized with thiopental have demonstrated increases mainly in plasma adrenalin as a result of haemorrhage (8) and rises in both noradrenalin and adrenalin during carbon dioxide accumulation (10). In this study an attempt has been made to assess whether sympathetic activity is depressed or abolished in dogs subjected to blood loss or hypercarbia during a steady state of halothane anaesthesia.

METHOD

After induction of anaesthesia in dogs with minimal amounts of thiopental (2.5 per cent), the trachea was intubated with a No. 10 cuffed rubber Magill tube, and positive pressure ventilation (+10 to 15 cm. H_2O) was started, using a Bird respirator (Marks 4 and 8) into which a 5 L./min. flow of 100 per cent oxygen was delivered; a Ruben valve prevented rebreathing. One femoral artery was cannulated for direct blood pressure recording and withdrawal of blood samples. Heparin (Connaught Laboratories), 10 mg./kg., was injected intravenously.

Following an initial period of ventilation with 100 per cent oxygen, during which further injections of thiopental were rarely required, control blood samples were withdrawn. These comprised 35 ml. for assay of plasma adrenalin and noradrenalin, essentially as described (9) and 8 ml. (withdrawn anaerobically) for determination of whole blood pH, pCO_2, and "standard" bicarbonate of plasma by the method of Astrup (1). Throughout every experiment an equal volume of normal saline solution was given intravascularly after each blood sampling.

Halothane was administered by redirecting the oxygen flow through a Fluotec vaporiser Mark II, which was set to deliver a 2 per cent or higher concentration. In twelve studies, blood samples were withdrawn after 30, 60, and 120 min. of uncomplicated halothane anaesthesia, during which respiration was controlled without the use of muscle relaxants. Thereafter, in seven experiments,

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10 or 20 per cent carbon dioxide in oxygen was delivered to the system via the Fluotec vaporiser, following which spontaneous respiration was resumed, usually in less than 1 min. Blood samples for laboratory estimations were then withdrawn after a further 15, 30, and 60 min. of anaesthesia. In the other five experiments, controlled ventilation with 2 per cent halothane in oxygen was continued while the animals were subjected to a haemorrhage of 20 ml./kg., followed later by a second haemorrhage of 12–18 ml./kg. Blood samples were withdrawn for estimation 15–20 min. after each haemorrhage. During the periods of hypercarbia or haemorrhage the inspired halothane concentration was not reduced except for brief periods when a state of extreme hypotension indicated that circulatory collapse was imminent.

Results

The first parts of Tables I and II show that during the 2-hour period of controlled ventilation with 2 per cent halothane in oxygen, preceding hypercarbia or haemorrhage, a moderate respiratory alkalosis was maintained with a quite constant level of pCO_2. During this steady state small increases and decreases in

TABLE I

Average Data, in Six Experiments during a 60 Min. Period of Hypercarbia following 120 Min. of Steady Halothane Anaesthesia

Time (min.)	pH	pCO_2 (mm. Hg)	"Standard" bicarbonate (m-mole/L.)	Adrenalin (μg./L.)	Noradrenalin (μg./L.)	Arterial B.P. Systolic (mm. Hg)	Arterial B.P. Diastolic (mm. Hg)	Heart rate
Control	7.50	28.3	21.1	0.22	0.30	154	92	101
+30′	7.53	29.2	22.6	0.39	0.26	101	57	94
+60′	7.51	27.6	20.7	0.32	0.57	98	55	94
+120′	7.51	25.5	20.1	0.33	0.28	100	60	89
			carbon dioxide (10 or 20%)					
+15′	7.03	113	24.4	0.71	0.93	105	49	115
+30′	6.97	141	25.4	1.9	1.3	106	45	114
+60′	6.94	153	25.7	3.6	1.7	105	46	115

TABLE II

Average Data, in Five Experiments, during a Period of Haemorrhage following 120 Min. of Steady Halothane Anaesthesia

Time (min.)	pH	pCO_2 (mm. Hg)	"Standard" bicarbonate (m-mole/L.)	Adrenalin (μg./L.)	Noradrenalin (μg./L.)	Arterial B.P. Systolic (mm. Hg)	Arterial B.P. Diastolic (mm. Hg)	Heart rate
Control	7.53	29.8	24.2	0.28	0.22	163	80	97
+30′	7.56	25.6	22.2	0.18	0.06	106	58	84
+60′	7.52	26.6	21.5	0.11	0.20	101	55	87
+120′	7.53	25.6	21.3	0.22	0.43	96	54	89
			haemorrhage					
+20′	7.48	25.2	18.7	0.70	0.32	60	28	88
+40′	7.37	25.8	15.2	7.5	0.94	28	13	103

plasma catecholamine concentration occurred in individual studies, but no consistent average trend could be measured, indicating either that smooth halothane anaesthesia with perfect oxygenation and with normal or reduced arterial pCO_2 was not accompanied by increased sympatho-adrenal activity, or that the changes which did occur were too small to be accurately assessed.

Table I shows the average values in six experiments when 10 or 20 per cent carbon dioxide was administered during halothane anaesthesia. The fall in pH, increase in pCO_2, and moderate rise in "standard" bicarbonate, changes characteristic of the acute respiratory acidosis, were accompanied by progressive increases in circulating noradrenalin and adrenalin which occurred in all six experiments. From average levels of 0.28 and 0.33 μg./L., at a pCO_2 of 26 mm. Hg, plasma noradrenalin and adrenalin increased to 0.93 and 0.71 μg./L. respectively at a pCO_2 of 113 mm. Hg, to 1.3 and 1.9 μg./L. at a pCO_2 of 141 mm. Hg, and at the final average pCO_2 of 153 mm. Hg plasma noradrenalin was 1.7 and adrenalin 3.6 μg./L. Average total plasma catecholamine concentration in all samples withdrawn during this hour of respiratory acidosis, 3.4 μg./L., was significantly higher ($p<0.05$) than the average level of 0.71 μg./L. during the previous 2 hours of uncomplicated halothane anaesthesia.

Arterial blood pressure, which was reduced during the steady state of halothane anaesthesia, showed variable changes when the arterial pCO_2 increased. The following *early* changes were observed in different experiments—an increased systolic and lowered diastolic pressure, a rise in systolic and diastolic, or a fall in both pressures. The effects seen with 10 per cent carbon dioxide were less pronounced than with the higher concentration. Thus, in one experiment 20 per cent carbon dioxide produced an immediate and progressive fall in blood pressure which was reversed by reducing the inspired halothane concentration from 2 to 1 per cent. In another experiment (the data from which are excluded from Table 1) there was an initial rise in systolic and diastolic pressures when spontaneous respiration started, but profound hypotension and apnoea then developed, the halothane concentration remained at 2 per cent, and circulatory collapse occurred 14 min. after starting 20 per cent carbon dioxide inhalation. Total plasma catecholamine concentration had increased from 1.3 μg./L. before hypercarbia to 4.4 μg./L. just prior to cardiac arrest. In the third experiment in which 20 per cent carbon dioxide was given there was an initial rise in systolic and diastolic pressures, and at a later period cardiac arrhythmias were noted, this being the only occasion in seven experiments when cardiac irregularities were observed on the blood pressure tracing as pCO_2 increased during halothane anaesthesia.

The most consistent circulatory changes when hypercarbia was established during halothane anaesthesia were a fall in diastolic pressure and an increased heart rate; changes in systolic pressure were more variable. Consideration of the data given in Table I shows that mean arterial blood pressure was *reduced* after 15, 30, and 60 min. of increased pCO_2 during halothane anaesthesia.

The effects of haemorrhage during halothane anaesthesia are shown in Table II; the data are averaged from 5 experiments. The gradual decline in pH and "standard" bicarbonate, at a constant level of pCO_2, demonstrates the metabolic acidosis induced by haemorrhage (5). Increases in plasma adrenalin occurred

but were not pronounced 15–20 min. after the initial blood loss of 20 ml./kg. After a second haemorrhage, which increased heart rate and reduced blood pressure to very low levels, average plasma adrenalin concentration had increased to 7.5 μg./L. The average circulating adrenalin level in all samples withdrawn during the steady state, 0.17 μg./L., was increased to 4.1 μg./L. during the period of haemorrhage. In one experiment the sympatho-adrenal response to haemorrhage appeared minimal, plasma adrenalin increasing from zero to only 0.32 μg./L.; by contrast, in another study a plasma adrenalin concentration of 26 μg./L. was reached. In the remaining three experiments the average adrenalin level increased from 0.32 μg./L. in all samples withdrawn during the steady state, to 2.3 μg./L. during the period of haemorrhage. The probability that samples for estimation were not always withdrawn at a time when sympatho-adrenal responses were maximal was shown by one experiment, in which a plasma adrenalin level after haemorrhage of 2.3 μg./L. was increased to 6.2 μg./L. after a further 12 min. without additional blood loss.

Because of the wide range of values measured in this small number of experiments (resulting in a large standard error) the increase in plasma adrenalin levels, although pronounced, was not significant at the 5 per cent level.

During halothane anaesthesia plasma noradrenalin showed much smaller increases in response to haemorrhage (Table II).

Discussion

The results obtained in this study with halothane agree with previous findings in dogs lightly anaesthetized with thiopental, namely that predominant increases in plasma adrenalin occur during haemorrhagic hypotension (8) while carbon dioxide accumulation induces rises in both noradrenalin and adrenalin (10). During the hypercarbia of diffusion respiration, at a pCO_2 averaging 173 mm. Hg in five experiments, average total plasma catecholamine concentration was 5.7 μg./L. (10). In the six experiments of the present study, at an average pCO_2 of 153 mm. Hg during halothane anaesthesia, total plasma noradrenalin and adrenalin concentration was 5.3 μg./L. There is clearly no evidence from the data that halothane reduces the sympatho-adrenal response to hypercarbia to an extent greater than that of light barbiturate anaesthesia.

A moderate fall in mean arterial blood pressure appears to be the usual response to established hypercarbia during halothane anaesthesia in dogs. Page and Olmsted (11), emphasizing the variability in response of arterial blood pressure to hypercarbia in anaesthetized dogs, found that controlled ventilation with carbon dioxide/oxygen mixtures during barbiturate anaesthesia produced either hypotension or hypertension initially, arterial pressure later returning to control or moderately increased levels. In regard to systolic pressure, the findings of the present study are similar, and failure of blood pressure to rise in response to hypercarbia during halothane anaesthesia cannot be interpreted simply as evidence of autonomic depression. Also, if ganglion blockade were an important or constant feature of halothane anaesthesia, *severe* hypotension might have been expected to occur as an immediate response to carbon dioxide in more than only

one out of seven experiments since the hypotensive response to carbon dioxide has been found to increase when sympathetic ganglia are removed (11).

The design and results of this small series of experiments permit only broad conclusions concerning the effects of anaesthetic concentrations of halothane on the reflex responses to hypercarbia and haemorrhage, but it is clear that depression of sympathetic activity cannot be assumed to occur during surgical anaesthesia with this agent. Although low blood pressure states unaccompanied by significant increases in circulating catecholamine concentration during uncomplicated halothane anaesthesia may suggest autonomic depression, the increased plasma catecholamine levels induced by hypercarbia and haemorrhage imply that hypotension is not necessarily a valid indication that central or peripheral autonomic pathways are blocked; if ganglion blockade does occur during halothane anaesthesia then it appears to be incomplete, as others have stated (2, 13), and as clinical observations have suggested (4).

Summary

In an attempt to assess the sympatho-adrenal responses to hypercarbia and haemorrhage during halothane anaesthesia, plasma adrenalin and noradrenalin concentrations were determined in dogs maintained in a steady state of anaesthesia by ventilation with 2 per cent halothane in oxygen. During uncomplicated halothane anaesthesia no significant increase or decrease in adrenalin or noradrenalin could be measured. Elevation of arterial pCO_2 was accompanied by significant rises in plasma catecholamine levels; mean arterial blood pressure was reduced during hypercarbia. Haemorrhage induced variable increases in adrenalin, with less effect on noradrenalin. The results indicate that depression of sympathetic activity cannot be assumed to occur during surgical anesthesia with halothane.

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Résumé

Dans le but d'évaluer les réponses sympathico-surrénaliennes à l'hypercarbie et à l'hémorragie au cours de l'anesthésie à l'halothane, nous avons recherché chez des chiens maintenus à des niveaux d'anesthésie constants, à l'aide d'une ventilation avec de l'halothane à 2% et de l'oxygène, les concentrations d'adrénaline et de noradrénaline plasmatiques. Nous n'avons pas observé, au cours de l'anesthésie sans complication à l'halothane, ni de diminution ni d'augmentation importante de l'adrénaline ou de la noradrénaline. L'élévation du pCO_2 artériel s'est accompagnée d'augmentations importantes dans le plasma des taux de catecholamine; au cours de l'hypercarbie, la pression artérielle moyenne s'est abaissée. L'hémorragie a entraîné des augmentations variables de l'adrénaline,

mais a produit moins d'effet sur la noradrénaline. Les résultats nous permettent de constater que, au cours de l'anesthésie chirurgicale à l'halothane, on ne peut pas présumer d'une dépression de l'activité sympathique.

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THE EFFECT OF HYPOTHERMIA AND OTHER FACTORS ON CEREBROSPINAL FLUID PRESSURE[1]

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HAEMODYNAMIC FACTORS have long been stressed as important in the maintenance of cerebrospinal fluid pressure. Percival Bailey stated that it was influenced by both arterial and venous pressure (1). The precise relationships, however, remain a matter of controversy and this applies, in particular, to the consideration of hypothermia.

The experimental reduction of cerebrospinal fluid pressure (2) and the clinical observation of a "slack" brain at operation with hypothermia has been well documented (3, 4). The extremely close relationship between cerebrospinal fluid pressure and venous pressure reduction during hypothermia was previously emphasized (2), but in our experiments this only occurred under specific circumstances. Both in normothermia and hypothermia the relationship of haemodynamic changes to cerebrospinal fluid pressure proved complex. Multiple simultaneous recordings demonstrated this complexity.

METHOD

Utilizing intravenous Nembutal®, the initial dose being 30 mg./kg., 33 dogs were surface cooled. Ten dogs were subsequently excluded from this series because they received other pharmacological agents, some of which produce direct haemodynamic changes (5). Eight additional dogs were subjected to repeated normothermic procedures mentioned below.

Temperature readings were obtained with a paracardiac intra-oesophageal thermistor. Pulse rate and aortic blood pressure were recorded by means of intravascular cannulation of the femoral artery rather than the carotid artery. This lessened the possibility of disturbing intracranial circulation (6). Venous pressure was recorded from the inferior vena cava via the femoral vein, jugular pressure being obtained only in certain experiments. This also lessened the possibility of disturbing cerebral circulation. Respiration was reflected in both venous and cerebrospinal fluid fluctuations. Either electromyography or electrocardiography was employed as supplementary measures for the detection of shivering or straining.

Cerebrospinal fluid pressure was recorded by means of a polyethylene catheter

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threaded caudally through the cisterna magna via a No. 15 needle. A wide bore catheter was used in order to show minor fluctuations (7). A 2-hour period of observation prior to hypothermia was essential to ensure that cerebrospinal fluid pressure was not falling because of leakage about the catheter.

Endotracheal intubation with pressure cuff was used in all dogs. For reasons to be discussed later, spontaneous respiration, supplemented by positive-pressure respiration when necessary, was the respiratory method of choice.

Temperature was usually not carried below 25° C. in the hypothermia experiments. The rewarming phase, which is not mentioned in many articles on hypothermia, was recorded in this series.

Quantitatively measurable values (respiration, pulse rate and arterial, venous, and cerebrospinal fluid pressures) were simultaneously recorded with a Grass polygraphic recording unit. The quantitative changes were then graphically illustrated as percentage changes of the initial values in order to compare our results with those of others (2). Examples have been selected for illustration and discussion.

Results

Hypothermia

The method of subarachnoid catheterization described proved to be a more benign and reliable procedure than that of metal needle placements and, in most

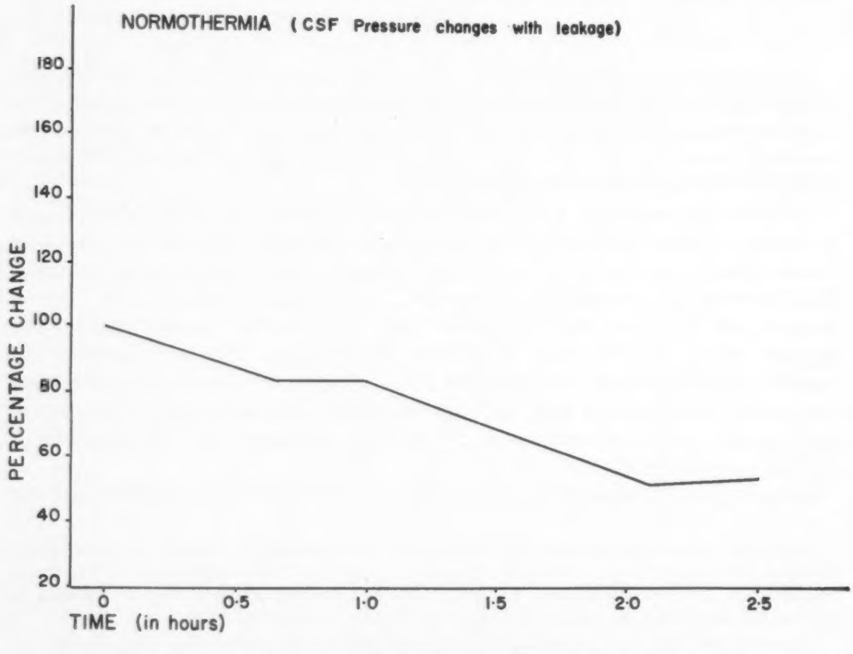

FIGURE 1. Normothermia (CSF pressure changes with leakage).

cases, cerebrospinal fluid leakage was avoided. An example with leakage, however, illustrates the necessity of the preliminary waiting period before proceeding with hypothermia (Fig. 1).

Using a previously described method of mechanical positive-negative respiration (2), we could not obtain completely satisfactory cerebrospinal fluid pressure reductions. The most satisfactory method finally evolved was one of spontaneous respiration supplemented, when necessary, by positive-pressure respiration at a rate previously found to maintain adequate oxygenation and fairly constant pH and pCO_2 at any given temperature (8).

Under "basal" conditions of hypothermia, that is, with adequate respiration and absence of straining or shivering, the results obtained tended to follow certain general trends which were graphically distinctive. Figure 2 is an example chosen to illustrate some of these features. In practically every experiment, arterial, venous, and cerebrospinal fluid pressure showed some transient initial increase with cooling and this occurred even when extremely large doses of Nembutal® were used. Subsequently, arterial pressure declined progressively. Venous pressure reduction, however, was generally less uniform but tended to approximate the arterial pressure reduction when the lower temperature ranges were reached. The final cerebrospinal fluid pressure reduction was greater than either the venous or the arterial pressure reductions. The pulse rate, following a short initial delay coincident with the rise of the above values, declined in a most constant and

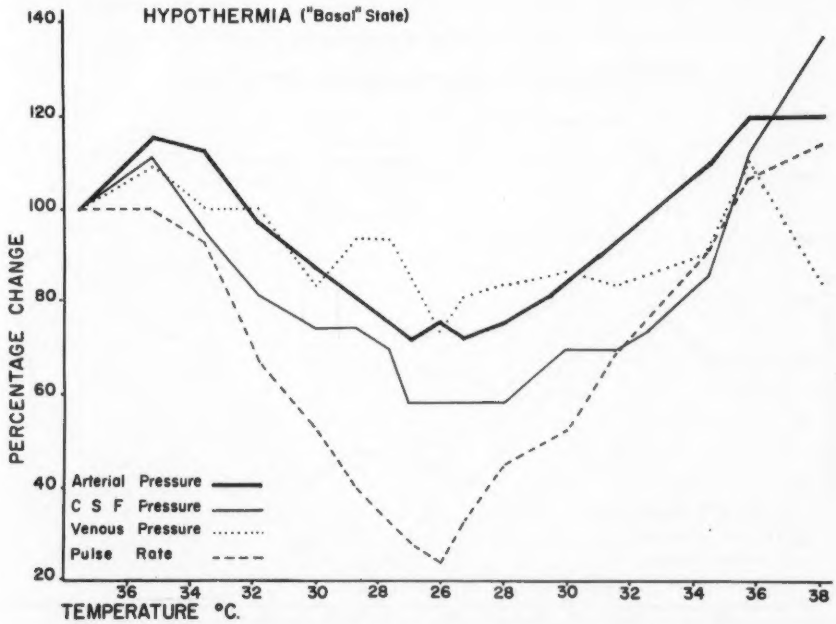

FIGURE 2. Hypothermia ("basal" state).

progressive manner. This feature of pulse rate change during cooling is comparable to the rate of decline previously recorded by other investigators (9, 10). An actual initial increase of pulse rate with cooling was not observed. Deviations from this pulse rate pattern occurred during circumstances associated with an inadequate "basal" state.

Figure 3 illustrates a recording that was obtained in the initial experiments, prior to the development of a reliable method of producing a "basal" state. With inadequate respiratory function there was a moderate increase of cerebrospinal fluid pressure, a marked increase of venous pressure and a slight increase in pulse rate. Cerebrospinal fluid and venous pressures were reduced by instituting assisted respiration.

Figure 4 is an example of the recordings obtained with mechanical positive-negative respiration. With this method of respiration there was only a moderate reduction of pulse rate, venous pressure, arterial pressure, and cerebrospinal fluid pressure.

Figure 5 illustrates another aspect of earlier experiments with inadequate respiratory assistance during cooling. The result was a minimal reduction in arterial, venous, and cerebrospinal fluid pressures and an inconstant pulse rate reduction. The onset of assisted respiration coincided with a definite decrease in venous and cerebrospinal fluid pressures. With inadequate respiration there usually was a fairly close relationship between venous and cerebrospinal fluid pressures.

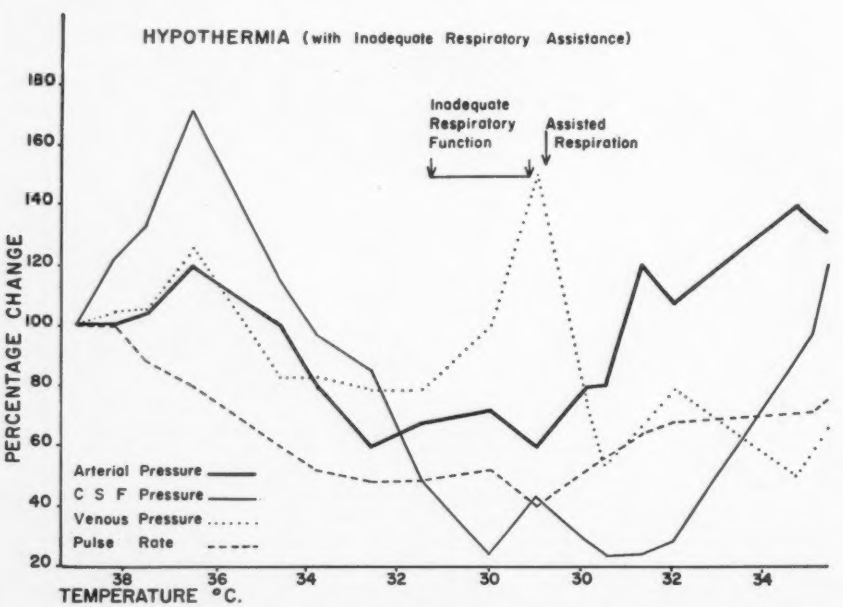

FIGURE 3. Hypothermia (inadequate respiratory assistance).

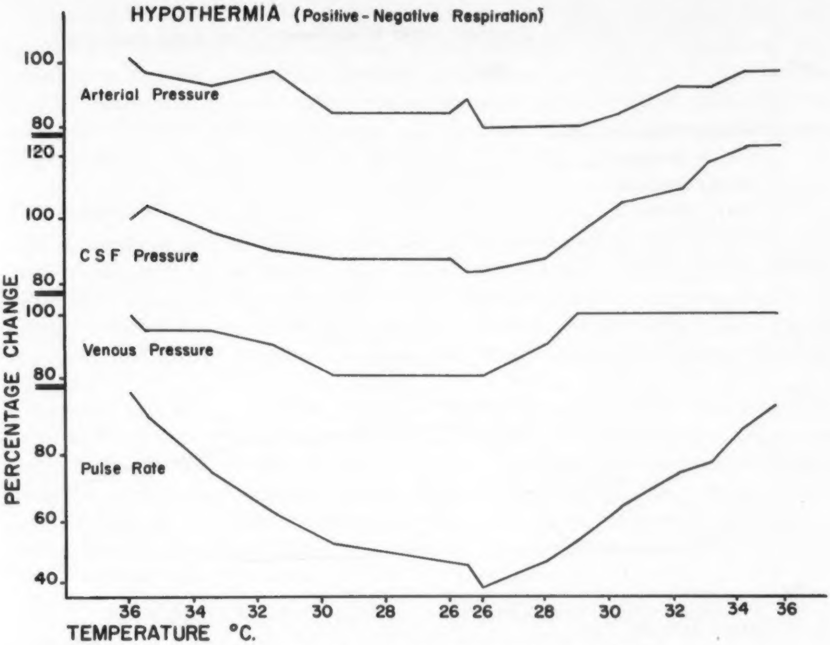

FIGURE 4. Hypothermia (positive-negative respiration).

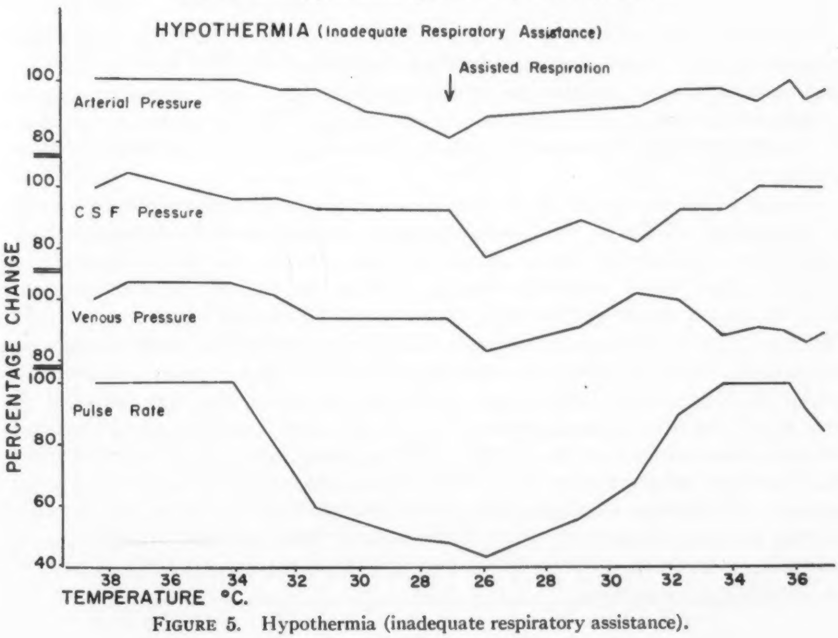

FIGURE 5. Hypothermia (inadequate respiratory assistance).

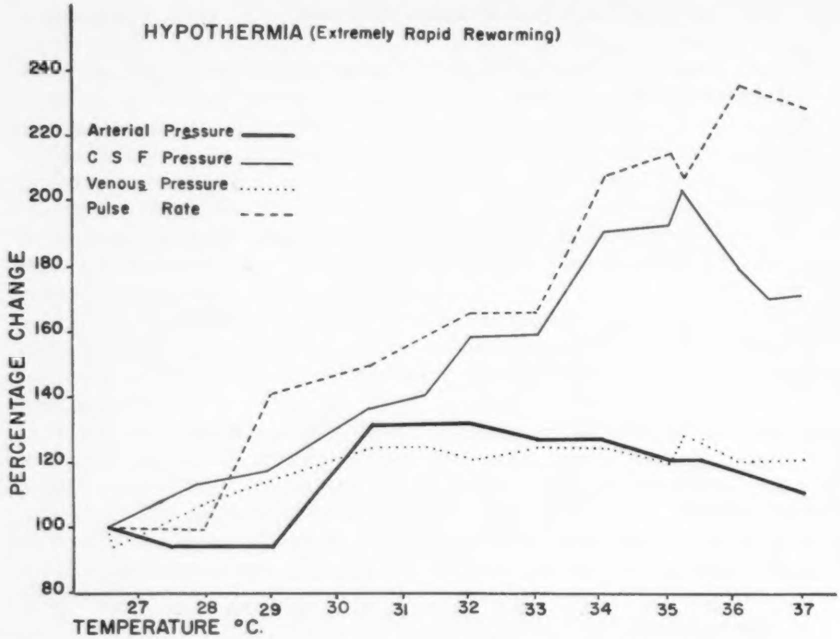

FIGURE 6. Hypothermia (extremely rapid rewarming).

Figure 6 is an example of a "shocklike" state that occurs with too rapid rewarming (11). There was a fairly close correlation between arterial pressure and venous pressure in this case. A rise in cerebrospinal fluid pressure occurred in spite of the declining arterial and venous pressures. In this particular instance of rewarming there was some relationship between pulse and cerebrospinal fluid pressures.

Perusal of the results obtained in the total group of hypothermia experiments demonstrated no simple relationship between cerebrospinal fluid pressure and pulse rate in either the cooling or the warming phases. Nor was it possible to obtain, under "basal" conditions during cooling, the almost identical relationships Rosomoff illustrated between venous and cerebrospinal fluid pressure (2). During straining, inadequate respiration, and with mechanical positive-negative respiration, however, there was a closer relationship between venous and cerebrospinal fluid pressures. Under these circumstances there was only minimal or moderate reduction of blood pressure and the decrease in cerebrospinal fluid and venous pressures was never marked. The greatest reduction of cerebrospinal fluid pressure occurred only when there was a substantial reduction in arterial pressure. At the lowest temperatures, the percentage reduction of venous pressure tended to approximate that of arterial pressure. When venous pressure rose at low temperatures, the increase in cerebrospinal fluid pressure was not as marked as at higher temperatures.

Although a fairly standardized method of rewarming was employed, each experiment produced some variation in the relationship of cerebrospinal fluid pressure to arterial and venous pressure and pulse rate (Figs. 2, 3, 6). One distinctive feature of the rewarming phase, however, was the very prominent dissociation of the cerebrospinal fluid and venous pressures in most instances (Figs. 2–6).

Normothermia

The questions raised by the normothermic experiments are being investigated further and will be elaborated upon in a future article. Some of the results, however, appear to be pertinent to the consideration of cerebrospinal fluid pressure during hypothermia in that they provide further illustration of the complex relationship between cerebrospinal fluid pressure and haemodynamic factors.

Figure 7 shows a marked reduction of cerebrospinal fluid pressure with Arfonad® induced arterial hypotension. There was a decrease in venous pressure, but it was not as marked as the reduction in arterial or cerebrospinal fluid pressure. Following excessive Neosynephrine® administration there was a marked increase of both cerebrospinal fluid and venous pressures. Experience with arterial hypotension in neurosurgery has confirmed this potential hazard of Neosynephrine administration.

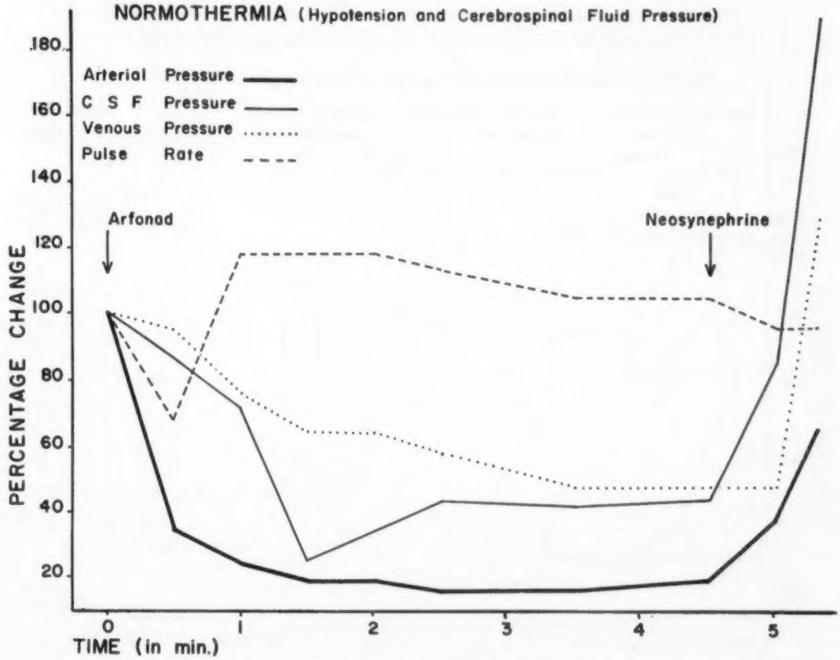

FIGURE 7. Normothermia (hypotension and cerebrospinal fluid pressure).

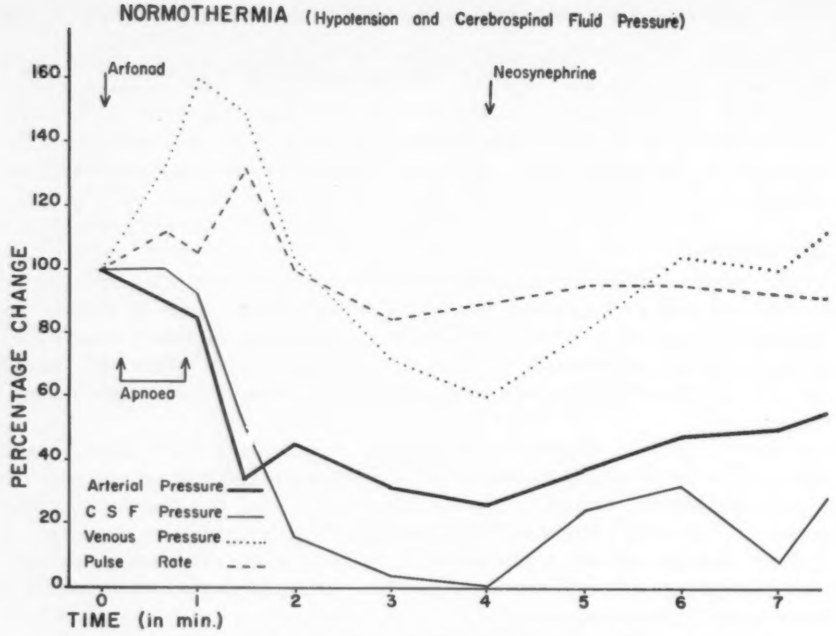

FIGURE 8. Normothermia (hypotension and cerebrospinal fluid pressure).

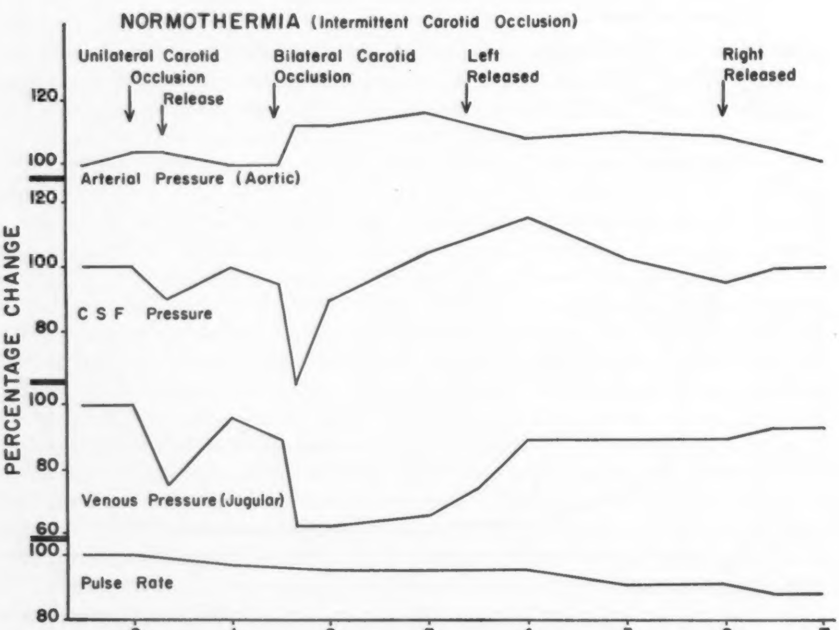

FIGURE 9. Normothermia (intermittent carotid occlusion).

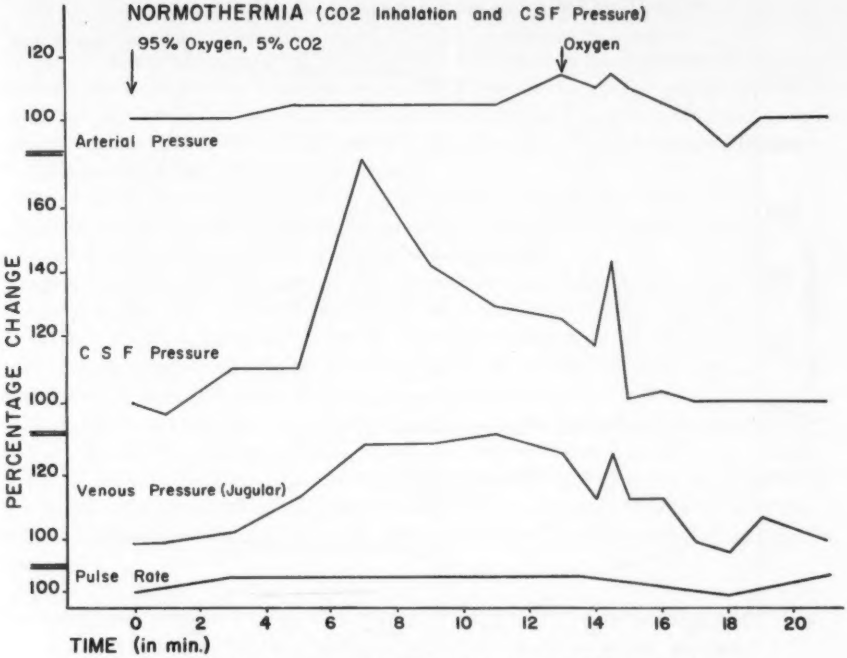

FIGURE 10. Normothermia (CO_2 inhalation and CSF pressure).

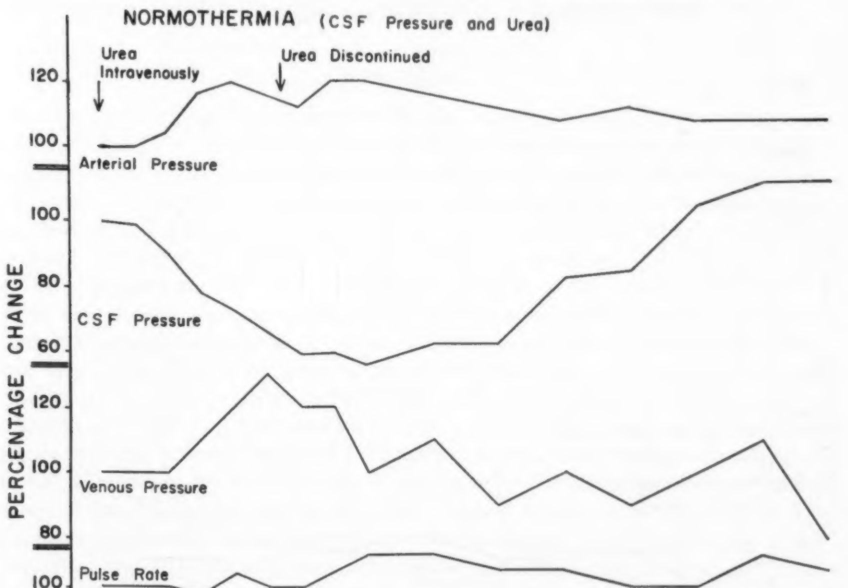

FIGURE 11. Normothermia (CSF pressure and urea).

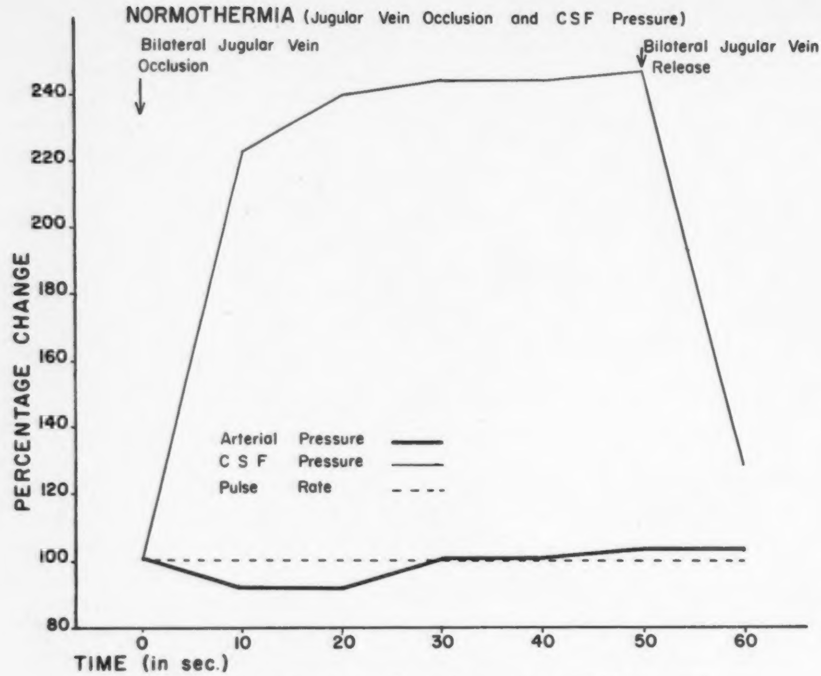

FIGURE 12. Normothermia (jugular vein occlusion and CSF pressure).

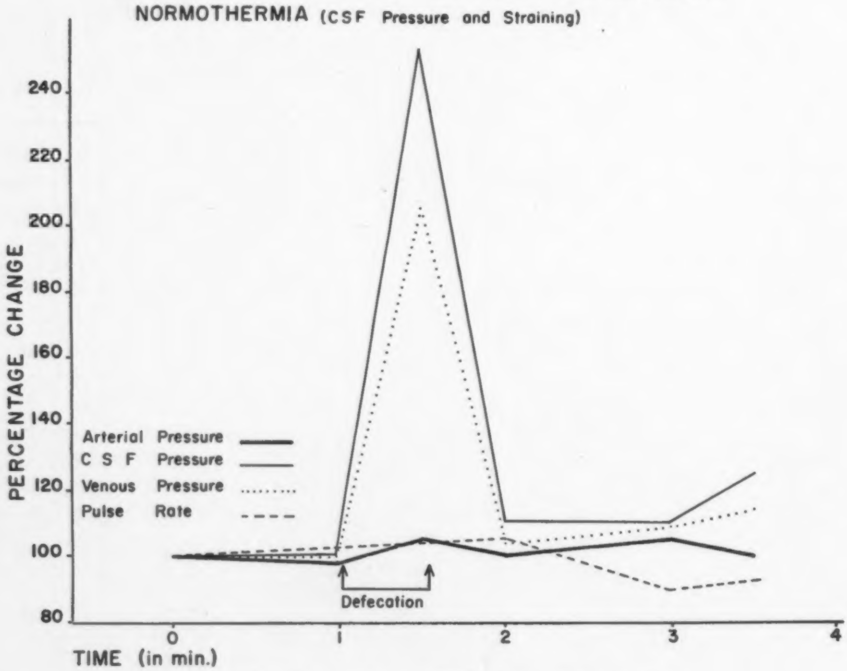

FIGURE 13. Normothermia (CSF pressure and straining).

Figure 8 illustrates a marked reduction of cerebrospinal fluid pressure following Arfonad administration. This reduction began while venous pressure was still rising during a period of apnoea. Slow administration of Neosynephrine produced a more gradual and less marked venous and cerebrospinal fluid pressure increase than that seen in the preceding example.

Figure 9 illustrates the importance of cerebral blood flow (volume) in the maintenance of cerebrospinal fluid pressure. The fall in cerebrospinal fluid pressure with bilateral carotid occlusion was dramatic.

Figure 10 illustrates the marked rise of cerebrospinal fluid pressure and jugular venous pressure with the administration of 5 per cent carbon dioxide and 95 per cent oxygen, a method known to increase cerebral blood flow by 75 per cent (12). Subsequently, there was a gradual reduction in cerebrospinal fluid pressure without a reduction in jugular venous pressure.

Figure 11 illustrates the marked but transient reduction of cerebrospinal fluid pressure with intravenous urea in spite of a rise of both arterial and venous pressures. The dosage and administration were according to Javid's method (13). Although not illustrated here, intravenous urea, combined with hypothermia, produced an extremely marked and sustained reduction of cerebrospinal fluid pressure.

Figure 12 illustrates the marked rise in cerebrospinal fluid pressure with bilateral jugular venous occlusion. Undoubtedly, this reflects increased intracranial blood volume and the clinical significance is obvious.

Figure 13 illustrates the close relationship between venous pressure and cerebrospinal fluid pressure with straining (defecation) during normothermia.

Discussion

The initial transient rise of arterial, venous, and cerebrospinal fluid pressures with cooling cannot always be explained by shivering alone (2) as in the "basal" experiments shivering and straining appeared to be completely absent. Lemmon and Davis (14) associated the rise of cerebrospinal fluid pressure with anaesthetic induction and intubation in their clinical hypothermia cases, but this was not applicable to our experiments as cooling was always delayed at least 2 hours following intubation. We have no adequate explanation for this phenomenon.

The complexity of factors influencing cerebrospinal fluid pressure has been illustrated in both normothermia and in hypothermia. During normothermia the close relationship between cerebrospinal fluid pressure and venous pressure during straining was readily demonstrated (Fig. 13). Unlike Rosomoff (2, 15), however, we could not demonstrate the exceedingly close relationship between venous pressure and cerebrospinal fluid pressure reductions during cooling under "basal" conditions. During the rewarming phase the cerebrospinal fluid pressure changes were frequently unrelated to the venous pressure change (Figs. 2–6). Therefore, in addition to venous pressure other haemodynamic factors should be stressed in the reduction of cerebrospinal fluid pressure during cooling and in its rise during rewarming.

Difficult as it is to prove conclusively, it is our impression that during cooling

the reduction of arterial pressure rather than venous pressure, is the more significant factor in the decrease of cerebrospinal fluid pressure. In addition, venous pressure reduction during cooling may be secondary to the arterial pressure decrease. During rewarming no simple and constant relationships were apparent.

During normothermia, however, the significant relationship of arterial pressure to cerebrospinal fluid pressure has been previously demonstrated. Using wide bore needles, O'Connell has shown marked variation, 5 to 50 mm. of water, in cerebrospinal fluid pressure coincident with heart beat, the cerebrospinal fluid pressure rising during systole and falling during diastole (7). Reduction of intracranial pressure during operation has been obtained with hypotension alone (16). We have demonstrated a marked reduction of cerebrospinal fluid pressure with experimental hypotension (Fig. 7) and that this can occur in spite of a marked rise in venous pressure is noteworthy (Fig. 8).

In addition, during normothermia, the profound decrease in cerebrospinal fluid pressure secondary to a diminution of cerebral blood flow has been shown (Fig. 9). By contrast an increase in cerebrospinal fluid pressure was observed coincident with a presumed increase in cerebral blood flow (Fig. 10). Rosomoff has demonstrated the progressive decrease in cerebral blood flow during cooling (17) but did not suggest any direct relationships between cerebral blood flow and cerebrospinal fluid pressure. Measurement of cerebral blood flow during rewarming would be of interest and the role of spinal blood flow as a factor in maintaining cerebrospinal fluid pressure has yet to be determined. Previous workers have emphasized the importance of cerebral blood flow in maintaining cerebrospinal fluid and intracranial pressure during normothermia (18, 19).

Finally, the possible factor of osmolarity must also be introduced in the consideration of cerebrospinal fluid pressure. With intravenous urea, both in normothermia and in hypothermia, there was a pronounced cerebrospinal fluid pressure reduction in spite of a rise in arterial and venous pressures (Fig. 11). During hypothermia there is a change in concentration of intravascular contents, but osmotic changes have not been precisely determined (20, 21). The possible role of osmolarity in the reduction of cerebrospinal fluid pressure during cooling warrants further investigation.

Conclusions

1. During cooling there are characteristic patterns of reduction of pulse rate and arterial, venous and cerebrospinal fluid pressures. Under conditions of adequate respiration and absence of straining or shivering, cerebrospinal fluid pressure reduction does not show a simple direct relationship to any of these factors. During rewarming, patterns of correlation are even less apparent.

2. Under certain circumstances of cooling such as straining, shivering and inadequate respiration, there is a close relationship between cerebrospinal fluid pressure and venous pressure.

3. A substantial reduction of cerebrospinal fluid pressure during cooling only occurs when there is an adequate reduction of arterial and venous pressures. Arterial pressure is probably the more significant factor.

4. During normothermia there is an important relationship between arterial pressure and cerebrospinal fluid pressure. Under certain circumstances there is also an important relationship between cerebrospinal fluid pressure and venous pressure, carotid blood flow and osmolarity.

5. The relationship of cerebrospinal fluid pressure to haemodynamic factors, both in normothermia and in hypothermia, remains complex.

Acknowledgments

We are deeply indebted to Mrs. M. Weishoff for her most able assistance in the laboratory and to Mr. R. Schneider and Mr. M. Wice for their technical aid in the recording of this data.

Résumé

Antérieurement on a affirmé qu'il existait une relation très étroite entre la diminution de la pression veineuse et la diminution de la pression du liquide céphalo-rachidien au cours du refroidissement, cependant nous n'avons pas réussi à établir l'existence d'une relation aussi étroite si la respiration est maintenue adéquate en évitant tout effort ou tout frisson. La tension artérielle, le pouls et la pression veineuse ont montré des tracés caractéristiques d'abaissement au cours du refroidissement, mais nous n'avons pas observé de corrélation exacte avec la diminution de pression du liquide céphalo-rachidien. Sur les tracés, les signes de corrélation étaient encore bien moins apparents au cours du réchauffement.

Toutefois, lorsque le refroidissement s'accompagnait d'efforts, de frissons ou d'une respiration inadéquate, nous avons observé une relation plus étroite entre les changements de la pression veineuse et ceux de la pression du liquide céphalo-rachidien. En ces circonstances, nous n'avons pas observé de diminution marquée de la pression du liquide céphalo-rachidien, de la pression veineuse, ni de la pression artérielle et, de plus, le rythme du pouls n'a pas diminué de façon progressive constante.

En général, on a noté une diminution importante de la pression du liquide céphalo-rachidien au cours du refroidissement seulement lorsqu'il existait une diminution adéquate de la pression artérielle et de la pression veineuse. Nous avons l'impression que, au cours de l'hypothermie, si la respiration est adéquate et en l'absence d'effort et de frisson, la diminution de la pression artérielle était probablement le facteur le plus indicateur de cette diminution de pression du liquide céphalo-rachidien.

En certaines circonstances de température normale, des relations entre la pression du liquide céphalo-rachidien, la pression artérielle, le débit sanguin cérébral et l'osmolarité (urée par voie intraveineuse) ont pu s'établir.

De toute façon, soit en présence de température normale, soit au cours de l'hypothermie, il semble complexe d'étalir des relations entre la pression du liquide céphalo-rachidien et les facteurs régissant l'hémodynamique.

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POST OCCLUSION HYPERTENSION AND PLASMA CATECHOLAMINE LEVELS[1]

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DURING HYPOTHERMIC anaesthesia for cardiovascular surgery, it has been noted that a hypertensive phase follows the period of circulatory occlusion. The hypertension is of abrupt onset and of variable degree and duration. Its characteristics have no obvious relationship to the type of cardiac lesion under repair, the presence or absence of vascular shunts, the duration of occlusion, or the degree of hypothermia. However, the hypertensive phase fails to occur when blood replacement is grossly inadequate or myocardial contractility is greatly diminished as with prolonged hypoxia, coronary air emboli and so forth.

Usually, there is a rise in the systolic and diastolic systemic pressures to approximately 160/110 mm. Hg and sometimes to much higher levels. Simultaneous observation of the pulmonary arterial pressures reveals an insignificant rise (<5 mm. Hg). With these considerations in mind it was decided to investigate the plasma catechol amine levels before and after the period of circulatory occlusion.

METHOD

Six children in good condition were selected (Table I). All had uncomplicated atrial septal defects of the secundum type which were repaired under direct vision during a period of circulatory occlusion. Hypothermic anaesthesia was conducted according to techniques previously outlined (1). The systemic blood pressure was monitored using a Collens oscillometer and an intra-arterial needle connected to a transducer and a Sanborn (150 M. series) six-channel recorder. Samples of blood (50 cc.) were withdrawn from the femoral artery with simultaneous intravenous blood replacement. Two samples were taken preceding the

TABLE I

Patient	Sex	Age (yrs.)	Weight (in lbs.)	Occlusion temperature		Duration of occlusion (in min.)	B.P. increase	
				Esophageal	Rectal		Systolic	Diastolic
1	M	6	32½	29.3	29.5	4	50	30
2	F	6	41	29.2	30.2	3.5	80	60
3	F	8	39	29.3	29.0	3.5	100	60
4	F	7	55½	30.0	31.0	3.0	50	40
5	F	12	64	30.5	31.1	4.0	100	35
6	F	7	37	31.7	31.2	5	55	40

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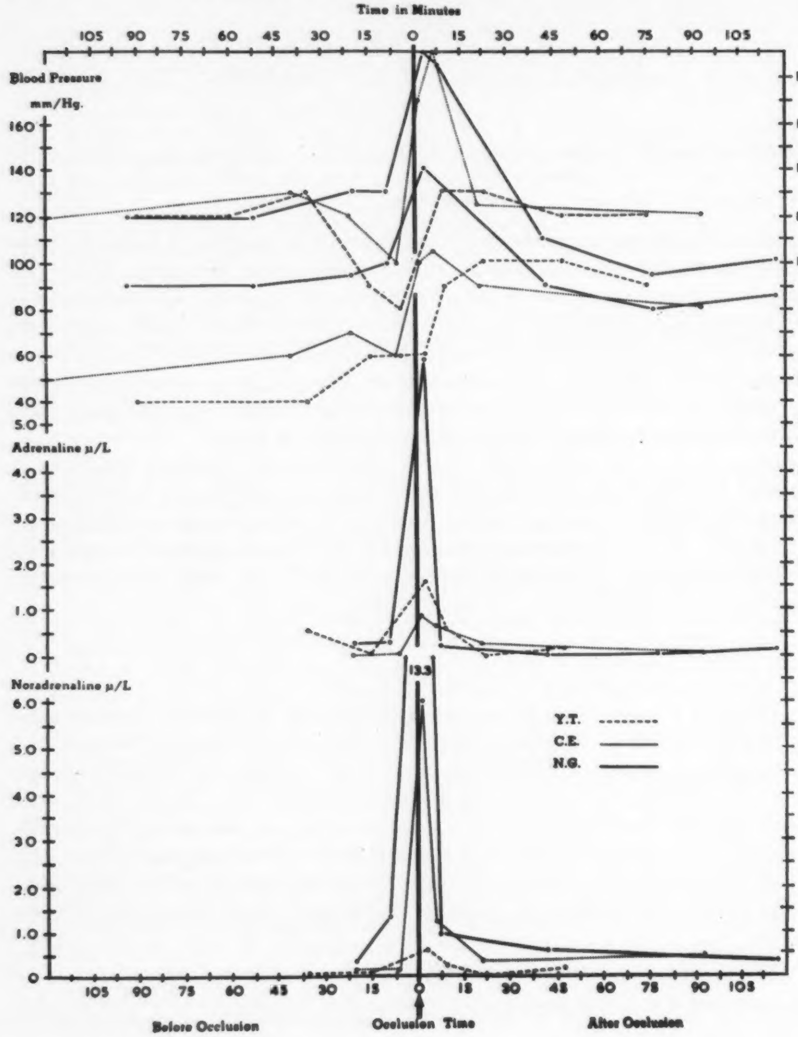
Time in Minutes
105 90 75 60 45 30 15 0 15 30 45 60 75 90 105
Blood Pressure mm/Hg.
160 140 120 100 80 60 40
180 160 140 120 100 80
Adrenaline µ/L
5.0 4.0 3.0 2.0 1.0 0
6.0 5.0 4.0 3.0 2.0 1.0 0
Noradrenaline µ/L
6.0 5.0 4.0 3.0 2.0 1.0 0
13.3
Y.T.
C.E.
N.G.
Before Occlusion
Occlusion Time
After Occlusion

FIGURE 1

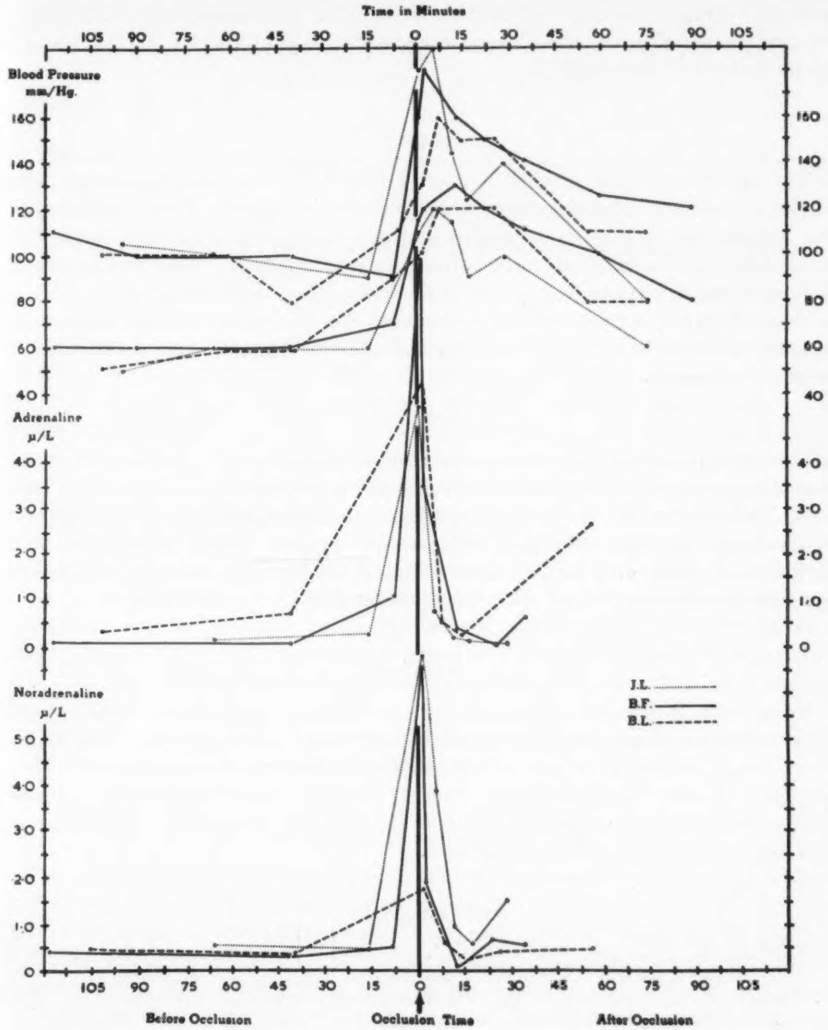
Time in Minutes
Blood Pressure mm/Hg.
Adrenaline µ/L
Noradrenaline µ/L
J.L.
B.F.
B.L.
Before Occlusion
Occlusion Time
After Occlusion

FIGURE 2

period of occlusion as controls, and the remainder were taken during the hypertensive phase. These samples were analysed by one of us (R. A. M.) using a method recently described (2).

Results

The results are illustrated in Figures 1 and 2 and are self-explanatory. The obvious relationship between the sudden increase in systemic blood pressure and the abrupt rise in plasma adrenalin and noradrenalin is apparent. Such high levels have only been encountered before in man in cases of phaeochromocytoma, although such levels are seen during haemorrhage and severe respiratory acidosis in dogs. Hypoxia is probably the major stimulus to release of these substances, but the exact mode of the stimulation and additional factors responsible remain to be investigated.

Summary

During hypothermic anaesthesia for cardiovascular surgery, it has been noted that a hypertensive phase immediately succeeds the period of circulatory occlusion. The mechanism of the hypertension was investigated in six patients by determining the adrenalin and noradrenalin plasma levels before and after occlusion. A close relationship was observed between the sudden increase in systemic blood pressure and the abrupt rise in plasma catechol amines.

Résumé

Nous avons remarqué que l'occlusion circulatoirre était suivie d'une periode d'hypertension dans nos cas d'hypothermie pour chirurgie cardiovasculaire. Nons avons recherché la concentration d'adrenaline et de noradrenaline plasmatique, avant et apris occlusion chez ces patients. Les résultats ont confirmé qu'il y avait une intime relation entre l'augmentation de pression artérielle et le taux des catecholamines dans le plasma.

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THE MANAGEMENT OF THE PATIENT WITH RESPIRATORY INSUFFICIENCY

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And the Lord God formed man of the dust of the ground and breathed into his nostrils the breath of life. ...

Genesis 2:7

Although Intermittent Positive Pressure (I.P.P.) respiration has been in use since Biblical times (1), methods of maintaining assisted respiration for prolonged periods were developed more recently. The prolonged use of I.P.P. was considered harmful to the lungs (2) and other methods were preferred (3–6). Of these, the cabinet respirator, in spite of certain disadvantages, achieved the greatest success. This was particularly so in the management of diseases producing muscular paralysis. However, in other conditions in which under-ventilation is a common cause of death, the use of the cabinet respirator was less successful.

In 1950, during a major epidemic of poliomyelitis, the prolonged use of I.P.P. provided satisfactory (7). This success led to the more frequent use of such techniques, which have been found applicable in a wide range of conditions. This paper presents a review of the management of such conditions, aided by experience with one hundred consecutive admissions to the Toronto General Hospital Respiratory Unit (8).

For the purposes of this discussion, Respiratory Insufficiency is present when underventilation endangers a patient's life.

Physiological Considerations

The main function of ventilation is to achieve oxygenation of the arterial blood and to eliminate carbon dioxide. Any depression of ventilation will lower the tension of oxygen in arterial blood (pO_2) and raise that of carbon dioxide (pCO_2). However, owing to the form of the oxygen dissociation curve in blood, ventilation must be quite markedly depressed before a fall in oxygen saturation occurs. Thus, a fall in saturation detectable clinically (or a significant fall in content measured manometrically) will not occur until the tension is reduced by nearly 50 per cent (9). Oxygen saturation or content is therefore a poor index of ventilatory efficiency. In contrast, arterial carbon dioxide tension and content show a very quick response to any ventilatory change. In patients with normal lungs and no vascular shunts, oxygenation will always be satisfactory when the pCO_2 is normal. The latter is therefore an excellent index of ventilation.

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Whereas a rise in inspired oxygen levels will improve oxygenation in most instances, even in the presence of respiratory insufficiency, carbon dioxide elimination is entirely dependent upon gaseous volume exchange. Thus, ***all patients with ventilation below normal will retain carbon dioxide, the effects of which are potentially lethal.*** To avoid the effects of carbon dioxide retention, the lungs of patients with respiratory insufficiency may be inflated with the necessary additional volume, by I.P.P.

The physiology of intermittent positive pressure ventilation must therefore be examined in an attempt to determine whether assisted ventilation, performed in this way, will produce adequate gaseous exchange and whether it will do so without embarrassing the circulation.

Gaseous Exchange

By creating a pressure gradient across the walls of the alveoli, positive pressure applied intermittently to the airway results in a flow of air and causes the lungs to expand. The volume of air entering the lung on each inflation will depend upon the pressure exerted (10). Pressures varying from 10–60 cm. H_2O above atmospheric, in the upper airway, may be necessary to deliver a normal tidal volume (V_T), depending on the extent of changes in total resistance due to pulmonary lesions. The higher figure is only necessary in rare instances such as severe bronchospasm or diffuse bilateral consolidation.

The adequacy of any given tidal volume will depend, in part, upon the size of the dead space.

Dead Space. The anatomical dead space is the volume of the airway from the point at which no rebreathing occurs down to the terminal bronchioles. While the former point is usually the mouth or nose, once the patient is connected to apparatus the dead space of the latter must be included. This will vary with each machine.

The significant or physiological dead space consists of the anatomical dead space, plus the volume of air entering any alveoli not being perfused by pulmonary capillary blood, plus any air entering perfused alveoli in excess of that necessary to achieve gaseous exchange. Adequate alveolar ventilation (V_A) begins once this dead space (V_D) is filled as shown in the equation $V_A = f\ (V_T - V_D)$ (f = resps. per min.). (At tidal volumes less than that of the dead space, the above equation is incorrect [11].)

A given minute volume is, within limits, better achieved by delivering large tidal volumes infrequently rather than the reverse, because of the need to overcome dead space on each inspiration (12, 13).

Nomograms are available for the determination of normal minute volumes in individuals in whom the physiological is equal to the anatomical dead space (14, 15). In patients with pulmonary lesions causing an enlarged physiological dead space, these figures will provide under-ventilation. This enlargement of physiological dead space is usually due to uneven distribution of inspired air throughout the lungs, causing uneven gaseous mixing.

Distribution. At one time it was believed that a gross distribution defect rendered I.P.P. for prolonged periods unacceptable (2). Although it has recently been con-

firmed that there is an increase in physiological dead space during I.P.P. (16) and that some mixing defect is inherent in this type of ventilation, it is now realized that this is of minor significance quantitatively.

Diffusion. It has been suggested the I.P.P. may produce a diffusion defect, either by trauma to the alveolo-capillary membrane or by reduction in pulmonary capillary flow. Diffusion defects have been demonstrated, however, only in post-thoracotomy patients where other aetiologies obtain (17). There is, in fact, circumstantial evidence to suggest that pulmonary capillary flow may be augmented at certain phases of I.P.P.

Defective diffusion of carbon dioxide is extremely rare, the more slowly diffusing oxygen being affected first. Thus a diffusion defect rarely demands increased tidal volumes, but always requires a raised oxygen content in the inflating gas.

Mechanics of Respiration

In normal spontaneous respiration, the work of breathing (18, 19) is performed by a muscular effort which creates a negative intrapleural pressure, with a resulting pressure difference across the alveolar wall. When this difference is sufficient to overcome the various resistances present, the lungs expand and air is drawn into the alveoli. The volume and distribution of this air depend upon the amount of muscular effort, the efficiency with which it is applied and the resistance offered.

Respiratory resistance consists of elastic and non-elastic elements (10). The former is produced by the elastic tissue of the lung and the chest wall (lung and thorax compliance), while the latter is produced by the inelastic tissues of the lungs and chest wall, the resistance to diaphragmatic movements, and the resistance to air flow. Through a normal respiratory cycle, air flow will vary from 0–40 L./min. at rest. Expiration is passive, the elastic forces overcoming the resistance to air flow.

Any change in resistance will require a similar change in the work of breathing if ventilation is to remain constant. Many patients are unable to increase their work of breathing and consequently underventilate as resistance rises. The most obvious change in mechanics during I.P.P. is that the work of breathing is taken over, on inspiration, either partially or completely by the ventilator. Passive expiration is usually left to the patient, unless a negative phase is introduced into the respirator cycle. Machines designed for I.P.P. respiration should be capable of performing work equal to any resistance likely to be offered in clinical practice.

Elastic resistance (compliance) has been shown to vary under certain circumstances of interest in connection with respiratory insufficiency:

A direct relationship has been shown between height, lung volumes, and compliance, except in neonates in whom the compliance is about half that seen at all other ages (20), and in whom it may be still lower in the presence of hyaline membrane disease (21).

The lung-thorax compliance is low in anaesthetized patients (22) and in anaesthetized paralyzed patients (23, 24). In the latter, it has been shown that both total and component compliances are reduced and that this is not related

to a rise in functional residual capacity. The reduction is related to a difference in distribution of the trans-alveolar pressure gradient by I.P.P. compared with normal spontaneous respiration (24).

A reduction in compliance has been shown in artificially ventilated poliomyelitics (23). In one series (25), it was observed that when spontaneous respiration was replaced by I.P.P. compliance and non-elastic resistance fell to approximately half the original value. Additionally, following I.P.P. during anaesthesia, using a respirator producing square wave respiration, a decrease in elastic recoil was noted (26).

Assuming the fall in compliance to be partly due to disuse, it has been suggested that it might be prevented in long-term respiratory insufficiency by daily inflation of the lungs to full volume. However, other reasons for the fall in compliance have been suggested (22, 23, 24).

Many other causes of raised resistance arise, bronchospasm, atelectasis, accumulation of secretions, consolidation or pulmonary oedema, and pleural effusions being well recognized. Any small increase in dead space or reduction in compliance produced by I.P.P. itself is of small importance, given a machine capable of delivering adequate volumes of gas.

Physiology of Breathlessness

Breathlessness is an important, if sometimes a misleading, symptom whose applied physiology is obscure. In the context of respiratory paralysis, uncomplicated by pulmonary disorder, circumstances can be created in which breathlessness is not an indication of underventilation, defined in terms of blood gases (27). For example, if such a patient is chronically overventilated, the addition of carbon dioxide to the inspired air, without alteration of rate or tidal volume, will give rise to the complaint of breathlessness while the pCO_2 is in the alkalotic range. Hence change, rather than absolute level of arterial pCO_2, is the stimulus causing change in the activity of the respiratory centre (28). Conversely, if the patient's tidal volume is reduced, he will complain of breathlessness before there is significant alteration of the blood gases. That is, mechanical stimuli alone will produce the symptom.

It is possible that breathlessness reflects a change in proprioceptive activity of muscles and that such a change may be induced by various means, mechanical and central. Central alteration of muscular activity via the muscle spindles is produced by change in the activity of the reticular formation of which the respiratory centre forms a part. Some such explanation is needed to account for the occasional anomaly in the occurrence and absence of breathlessness.

Cardiovascular Effects

An intermittent rise in intra-alveolar pressure, rather than a fall in intrapleural pressure, might be expected to reduce venous return and, consequently, cardiac output. However, it has been shown that provided ventilation is achieved by means of a respiratory pressure wave producing a low mean intrathoracic pressure, cardiac output does not fall and may even rise (29). The cause of this rise is not

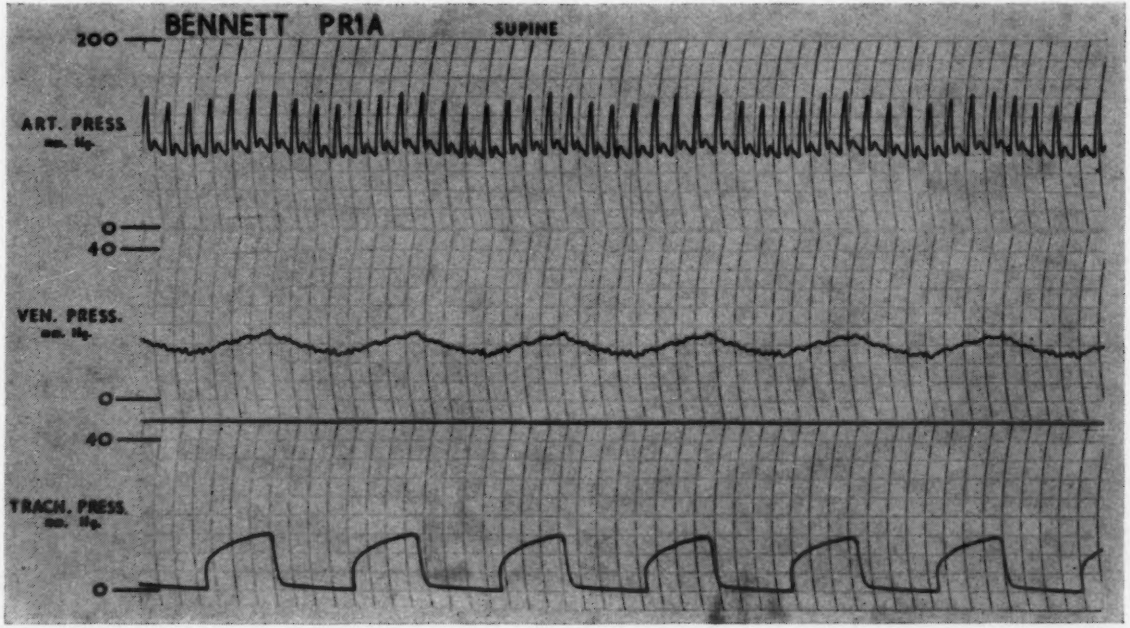


FIGURE 1. Variations in femoral artery and mean external jugular vein pressure during I.P.P. with machines producing different airway pressure curves. (Marker line between venous and tracheal pressures.)

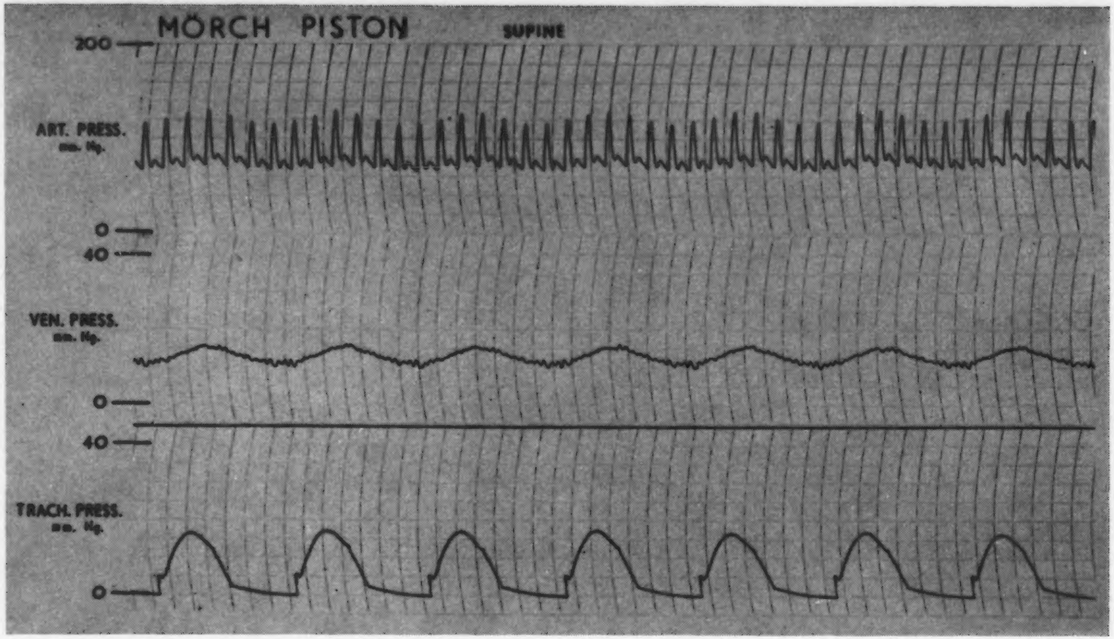


FIGURE 2. Variations in femoral artery and mean external jugular vein pressure during I.P.P. with machines producing different airway pressure curves. (Marker line between venous and tracheal pressures.)

known, but it is of interest that modern respirators usually produce variations of systematic blood pressure within each respiratory cycle, the peak occurring at the point of maximum inflation pressure (Figs. 1 and 2). This may be due to improved left ventricular filling during a relatively short inflation phase. It has been suggested that this may be related to an increase in expanded lung, opening an unusual number of pulmonary capillaries, or to an increasing ejection of blood from the lungs through the course of each inflation. Thus, I.P.P. would convert the lungs into an auxiliary pump, filling during expiration and pushing blood into the left heart on inflation. Provided that the point of maximum efficiency was not exceeded then, the heart action would improve and the stroke volume increase (Starling's Law). In the event of hypovolaemia, I.P.P. lowers cardiac output, and this reduction may be reversed by introducing a negative phase to the respiratory cycle (30).

There is thus the concept that each inflation reduces venous return but that this is offset by the ejection of blood from the lungs. If blood volume is low, the effect on venous return is greater and the intra-pulmonary blood volume less. Consequently, the reduction in venous return then has the predominant effect on cardiac output.

While the effects of I.P.P. on cardiac output predominate in variations in systemic blood pressure, the calibre of systemic vessels also varies with airway pressure (31–34) and with blood and tissue gas levels. The diameter of pulmonary vessels varies with the oxygen tension of blood perfusing chemoreceptors in the carotid and aortic areas and, possibly, with carbon dioxide tension (35, 36).

Acid-Base Balance

The effects of I.P.P. on acid-base balance will depend primarily upon alveolar ventilation and secondarily upon renal function. In conditions of ventilatory instability 50 per cent of the change in body CO_2 levels will occur within four minutes of changing ventilatory volumes (37).

In the treatment of patients previously in chronic respiratory acidosis it may take several days for the metabolic compensation to adjust. In such instances, reduction of the arterial pCO_2 to normal will produce marked alkalosis. This has been noted in the presence of satisfactory renal function and in part may reflect the lag between the more rapid changes in labile forms of plasma carbon dioxide and the slower changes in tissue carbon dioxide stores.

Certain of the physiological problems encountered in the commoner causes of respiratory insufficiency will be discussed below, in association with their clinical management.

Indications for Assisting Ventilation

The main indication for assisting ventilation is the presence of respiratory insufficiency due to a reversible condition. There are many such conditions other than those producing muscular paralysis and I.P.P. has been used in all. Other

circumstances are, for example, to rest the respiratory muscles in a patient with advancing poliomyelitis, to prevent or relieve exhaustion from the work of breathing, and to prevent paradoxical movement of the chest wall. Finally, under some circumstances it is indicated as a means of delivering 100 per cent O_2 for short periods.

The conditions in which underventilation may arise are exemplified in the following list:

(*a*) *Conditions obstructing the airway*, for example haematomata, inflammation of the upper airway, oedema, bulbar palsy, excessive secretions. This group is treated by relieving the obstruction but in the event of hypoxia, hypercarbia, and exhaustion, a period of respiratory assistance is often valuable.

(*b*) *Neuromuscular disorders*, for example, head injuries, overdosage of narcotics or hypnotics, brain stem lesions, cervical cord lesions, poliomyelitis, polyneuritis, myasthenia gravis, disorders of potassium metabolism, and so forth.

(*c*) *Following the use of relaxant drugs*, usually in the treatment of status epilepticus or tetanus.

(*d*) *Pulmonary diseases*, for example, emphysema, bronchiectasis, pneumonia, atelectasis, fibrosis, and left heart failure.

(*e*) *Disorders of the thoracic walls*, stove-in-chest, post-thoractomy, post-laparotomy, paralytic ileus, ankylosing spondylitis or kypho-scoliosis, extreme weakness due to debility.

Many of these conditions occur together. For example, a patient with ankylosing spondylitis may be precipitated into respiratory failure by pneumonia or by limitation of diaphragmatic movement and of coughing after laparotomy.

The *clinical picture of underventilation* is not uniform and varies with the condition which gives rise to it. Further, a perusal of the list will show how many other possible causes there may be of symptoms and signs such as disorder of consciousness, breathlessness, changes in pulse and blood pressure, often held to be characteristic of underventilation. This fallibility of clinical diagnosis is such that awareness of the possibility is the most important clinical factor and any suspicion should be promptly confirmed or rejected by measurement of the ventilation. Nonetheless, the clinical picture of acute underventilation demanding immediate treatment is characteristic, although uncommon. Extreme distress, sweating, cyanosis, violent respiratory efforts, tachycardia, hypertension proceed rapidly to coma, hypotension, gasping respiration, and death. The early stages have been called the Alarm Syndrome.

Similarly, chronic respiratory acidosis has characteristic clinical forms. The best known of these is the familiar aspect of the patient with advanced emphysema. Less well known is the presentation as a neurological syndrome (38) made up of headache, disorder of consciousness, papilloedema, involuntary movements, and a variable rigidity. These signs vary in prominence from case to case. A syndrome has also been described in which the patient appears partially curarized (39). This is probably non-specific and a similar picture has been described in association with marked metabolic acidosis (40).

It must be reemphasized that the pitfalls of diagnosis and of differential

diagnosis are such that, in most cases, measurement of ventilatory volumes, with or without measurement of the blood gases, is essential.

Ventilatory Measurements

The clinical suspicion that underventilation is present may be confirmed by measuring ventilation itself.

Tidal volume. This may be measured in one of the following ways. (i) Spirometry—this is most applicable in the conscious unassisted patient. However, it is cumbersome and requires special measures to overcome problems of carbon dioxide retention and expiratory resistance. (ii) Collection of expired gases, via a non-return valve (41) in a Douglas or plastic bag (42, 43). This also is somewhat cumbersome and still requires that the collected gas be measured by passing it through a spirometer or gas meter. (iii) Dry Gas Meter—this is a relatively accurate method of measuring expired gas volumes. The apparatus looks and functions in the same way as a domestic gas meter. By means of a non-return valve, expired gas is fed through the meter for one or more minutes, respirations counted, and a mean tidal volume calculated. (iv) Ventilation Meters—these are perhaps the most convenient means of measuring expired gas volumes. The gas passes directly through them, turning a system of vanes. Reasonable accuracy is attained at all except the lowest gas flows. The most recent of these, the Wright Anemometer (44) (Fig. 3), can be placed in continuity with the airway, measuring gases passing in one direction only, and offering minimal resistance. It is extremely small and portable, the face being the size of a large wrist watch. The main objection to this type of equipment has been the fragility of the last named and the possibility of moisture from humidifiers altering the response of the vane and therefore the accuracy. More rugged but less easily manipulated are the Draeger and Monaghan meters (41).

By means of equipment of this type, the patient's tidal volume may be followed. Expired volumes are chosen as these are the more reliable when using I.P.P. Under such circumstances, some of the inflation volume may leak out between being measured and passing into the bronchi, whereas all the measured expired volume must come from the tracheo-bronchial tree. Comparison with a ventilation nomogram and consideration of the possibility of an enlarged physiological dead space will determine the likely adequacy of ventilatory exchange.

Having confirmed one's clinical impression by measuring ventilatory volume, any remaining doubts may be cleared by measuring arterial pH and CO_2 levels, which provide the only absolute guide to respiratory status (45). It should be stressed that CO_2 levels alone are not always sufficient owing to the not infrequent coincident metabolic changes in seriously ill patients.

Blood gas measurement. Arterial pCO_2 may be measured as follows:

(1) Directly (46, 47). This is technically difficult and not available in the average hospital laboratory.

(2) Derived from:

(i) ph and CO_2 content of arterial blood (48);

(ii) pH of arterial blood and pH of the same sample after equilibration with a gas of known pCO_2 (49);

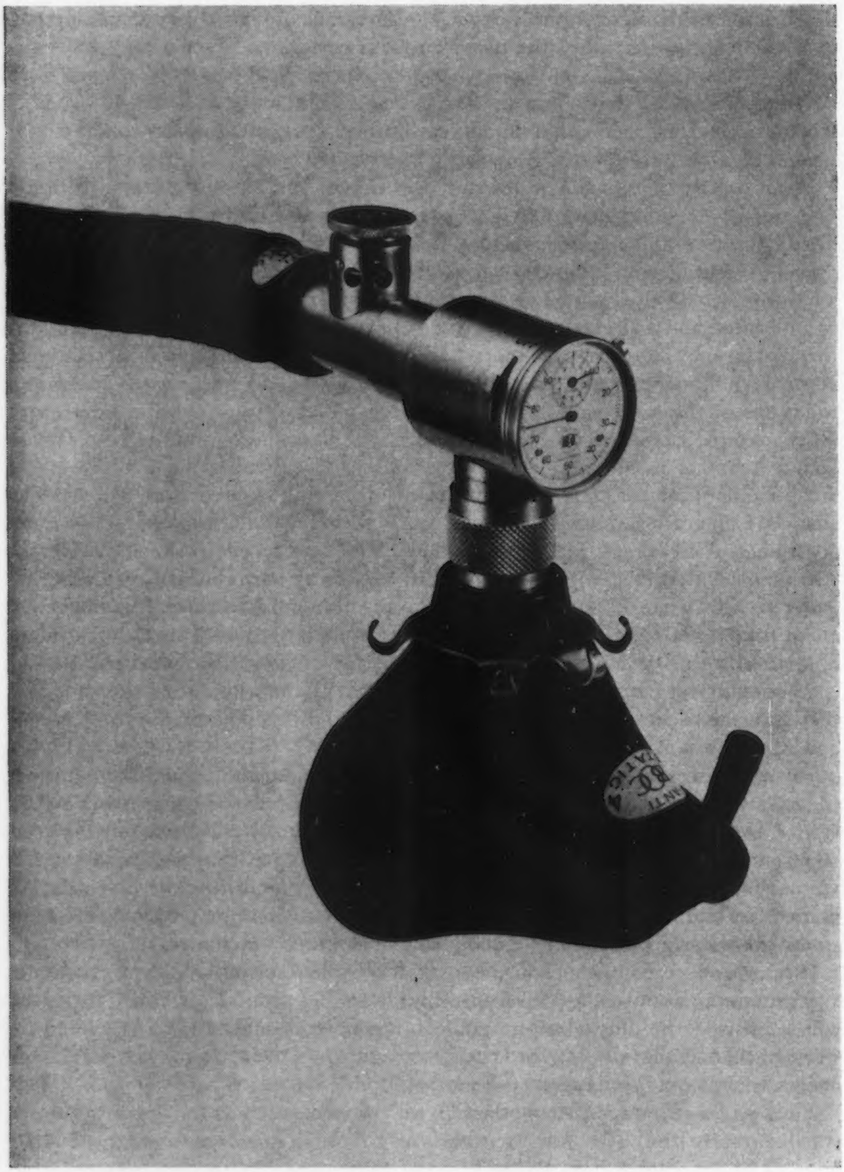


FIGURE 3. Wright Anemometer (connected to Magill semi-open system).

(iii) Alveolar gas sample, by single prolonged expiration or by modifications of the Plesch method (50–53), the gas being analysed by Haldane (47) or Scholander (54) apparatus, infra-red analyser (55–58) or one of several other more simple but, in most instances, less accurate methods (59–62). One of the latest of these methods has the merit of simplicity and relative accuracy (52) but all require an additional pH value for a complete picture.

(3) Assumed from:

(i) CO_2 combining power. This is essentially a measure of slowly changing metabolic factors. It is relatively valueless in acute respiratory problems and in the presence of combined metabolic and respiratory disorder (45). It may indicate the trend in chronic respiratory states. To derive maximum benefit from this estimation, within its limits, it should be considered in association with a pH value;

(ii) Arterialized venous samples (63, 64). When the forearm and hand are warmed and venous blood is taken from the dorsum of the hand, without tourniquet, good correlation with arterial values is obtained in normothermic normovolaemic patients;

(iii) End-tidal samples (65–67). Continuous readings may be made of the carbon dioxide levels in end-tidal air, using infra-red or photochemical principles. This value will follow that of the alveolar air if the tidal volume remains constant, but the absolute level will be of no special significance when measured alone.

Thus, arterial carbon dioxide levels may be determined by one of a number of procedures, of which the Astrup method has been found very satisfactory (method 2 (ii) above). A specialized virtue of this technique lies in the possibility of its use in patients recently given a volatile anaesthetic agent and the simultaneous availability of a pH value.

Oxygen administration. One must consider under what circumstances oxygen should be added to the inspired air. If a patient has normal lungs, this will not be necessary. However, any suspicion of a distribution or diffusion defect will indicate the addition of oxygen. I.P.P. creates one of the few circumstances in which 100 per cent oxygen may be delivered to the lungs for a prolonged period and the harmful effects of this should be remembered (68).

When adding oxygen to an apparatus delivering air, it may be difficult to assess the effectiveness of this addition. Improvement in oxygenation may be shown by a slowing of the heart rate but more reliable information may be obtained by (i) analysis of inspired or expired air by oxygen analyzer (69), (ii) oximetry (70–72), or (iii) intermittent arterial sampling and manometric analysis (73). In cases of marked desaturation, one may increase the flow of oxygen until no further improvement occurs in (ii) or (iii). In this way, maximum efficacy is achieved without the possibility of oxygen toxicity.

Clinical Application of Measurements

The way in which the measurements of respiratory volumes and blood gases are used in clinical practice is as follows:

(*a*) *The initial decision to ventilate.* In all cases not *in extremis*, ventilation is measured. The conscious patient is asked to breathe through a mouthpiece into

one of the measuring devices described above, after the application of a nose-clip. In the unconscious subject, nose-clip and large-flanged mouthpiece, facepiece, or cuffed endotracheal tube may be used. Values obtained are compared with a ventilation nomogram, and the first of a series of values is thus available. The decision to ventilate may be made on the basis of unequivocal underventilation shown on the first reading, or as a result of gradual deterioration as indicated by serial reading .

Unless ventilation is very obviously adequate, the arterial pCO_2 is then determined. Underventilation, as shown by tidal volume and arterial pCO_2, is taken as an absolute indication for assisted respiration except in two circumstances: (i) chronic respiratory acidosis with no evidence of recent deterioration and without trial of less drastic measures; (ii) minor degrees of acute respiratory acidosis in a rapidly improving situation, for example, recovery from deep anaesthesia.

(*b*) *Monitoring of efficiency of assisted respiration.* During I.P.P. the following measurements are made, in addition to routine clinical observations: (i) tidal volume, (ii) inflation pressure, (iii) arterial pCO_2. The volume necessary to achieve a normal arterial pCO_2 is noted at the outset and the pressure necessary to achieve this volume is observed. Frequent measurements of ventilation will be needed in the acute stages.

Further arterial pCO_2 values will be obtained only when doubt exists as to the respiratory status, for example, in managing patients with gross pulmonary disease or as a very occasional check in patients needing prolonged treatment.

Management of Airway and Ventilation

The equipment necessary for the management of respiratory insufficiency by I.P.P. may be grouped as follows: airway and suction equipment; non-return valve; humidifier; ventilator.

AIRWAY. A small group of patients can be managed satisfactorily by means of a face-mask or nose-clip and mouthpiece, using no artificial airway of any sort. These are conscious patients with chronic respiratory disease and considerable insight. With a little training, they can use I.P.P. in this way to deliver bronchodilators, vasoconstrictors, and wetting agents (74, 75). Improved bronchiolar calibre and elimination of secretions may then improve ventilation. Such therapy has usually proved impracticable in the treatment of severe respiratory insufficiency and lends itself more to the less severely affected group of patients with chronic respiratory disease.

It is obligatory to create an airway and start ventilation as soon as underventilation is recognized. Even brief delay may result in cardiac arrest. The usual practice is to pass a cuffed orotracheal tube, a tracheostomy being performed subsequently if required. Tracheostomy is considered to be indicated when it is evident that the problem cannot be corrected within an arbitrary 24–48 hours. When early recovery is probable (e.g., barbiturate poisoning), tracheostomy is postponed. In all other cases, it is best delayed until resuscitation has been carried out, when the patient will be adequately ventilated, hydrated, and, if necessary, transfused and digitalized.

In all cases not *in extremis*, intubation is carried out under a minimal dose of sodium thiopentone and succinylcholine, using careful topical anaesthesia. If thiopentone is contra-indicated, the technique depends on the patient's level of consciousness. Thus, if amnesia is probable, muscle relaxant and topical anaesthesia are used. If the patient is more conscious, topical anaesthesia is used alone, in which case transtracheal instillation is preferred.

The need for great gentleness and maximal relaxation is emphasized by the occurrence of post-intubation granulomata of the vocal cords in two cases in which technical difficulty arose. Relaxants were not used and in one case the tube was only in place eight hours.

Once the airway is secure, the patient is sedated until he becomes accustomed to his new circumstances. In many instances he will become very much less agitated once adequate ventilation is established. However, in rare instances where sedation does not settle the patient and adequate ventilation cannot be achieved, muscle relaxants may be required as a temporary measure.

Tracheostomy. The virtues of tracheostomy in the treatment of respiratory insufficiency are as follows:

(i) Access for I.P.P.

(ii) Access for suction.

(iii) Protection from aspiration of pharyngeal secretions by using a cuffed tracheostomy tube.

(iv) Freedom from equipment about the mouth and nose, permitting the use of duodenal tubes, normal eating and drinking, and so on.

(v) Reduction of dead space. The latter factor is offset, when using I.P.P., by the added dead space of the apparatus and by the increase in physiological dead space produced by I.P.P. itself (16).

I.P.P. is not possible in conjunction with the usual types of tracheostomy tube, without an adaptor which fits into their lumen. This reduces the diameter of an already narrow airway.

Special equipment is usually preferred and a variety of tubes has been described. They should (*a*) be of adequate diameter (from 9–12 mm. internal diameter for adults), to minimize resistance to gas flow and to decrease the likelihood of obstruction by secretions, and (*b*) have adequate connections for attachment to I.P.P. equipment. The latter should not narrow the lumen and should be moveable through 360° (e.g., metal to metal slip-joint), in order that the I.P.P. equipment can remain stationary when the patient is moved.

Two main types of tracheostomy tube are in use: those with and without inflatable cuffs. The latter (76, 77) are less versatile, do not permit measurement of ventilation, and do not prevent aspiration of secretions from the pharynx. However, they have been advocated in the treatment of stove-in-chest by induced respiratory alkalosis (78). They are also of value in the management of tracheal ulceration secondary to over-inflation of cuffed tubes.

Cuffed tracheostomy tubes may be improvised by stretching a latex cuff over a large tracheostomy or laryngectomy tube but are also commercially available with an incorporated cuff. The former are usually made of metal or plastic and have the advantage of an inner cannula. However, the metal tubes usually leak

between the inner and outer cannula. They are inclined to be short and in a thick-necked patient or in one with oedema, haematoma, or surgical emphysema the cuff may lie in the extra-tracheal layers or the connector becomes buried below skin level.

The tubes made for I.P.P. are usually of rubber and vary in design (79, 80). Our experience has been that a gradual curve permits easy passage of a suction catheter, that a seamless cuff permits the tube to lie centrally in the trachea (Fig. 4), reducing the chance of mucosal ulceration, and that an open end, without built-in connector or flange, permits adjustment to the individual's neck thickness. To avoid the connector pulling out, a modification of the Nosworthy connector, onto which a flange has been built, has been designed (Figs. 5 and 6). This stabilizes the whole tube.

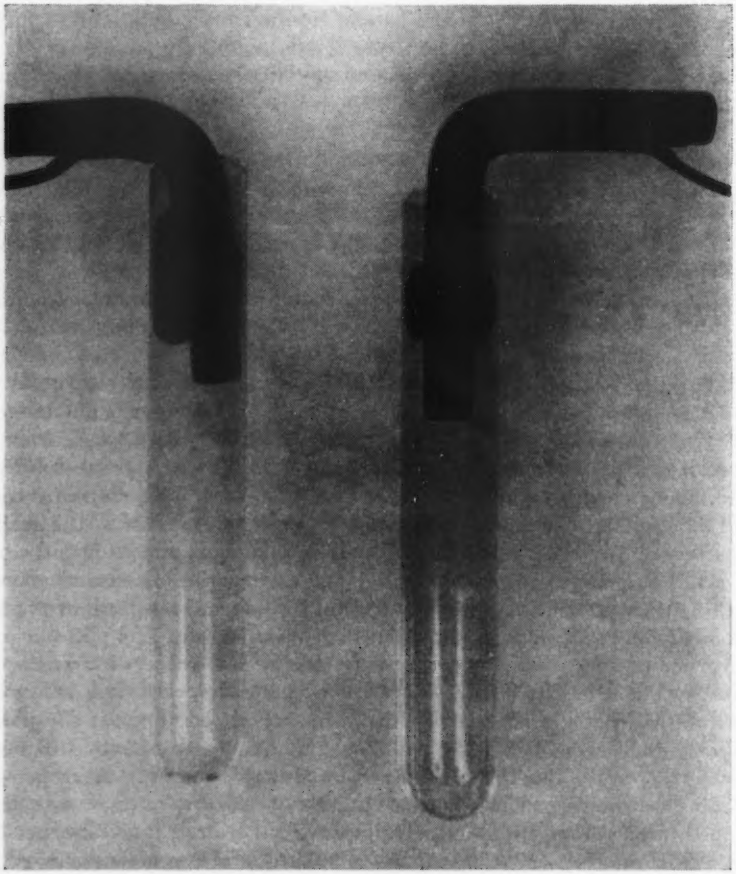
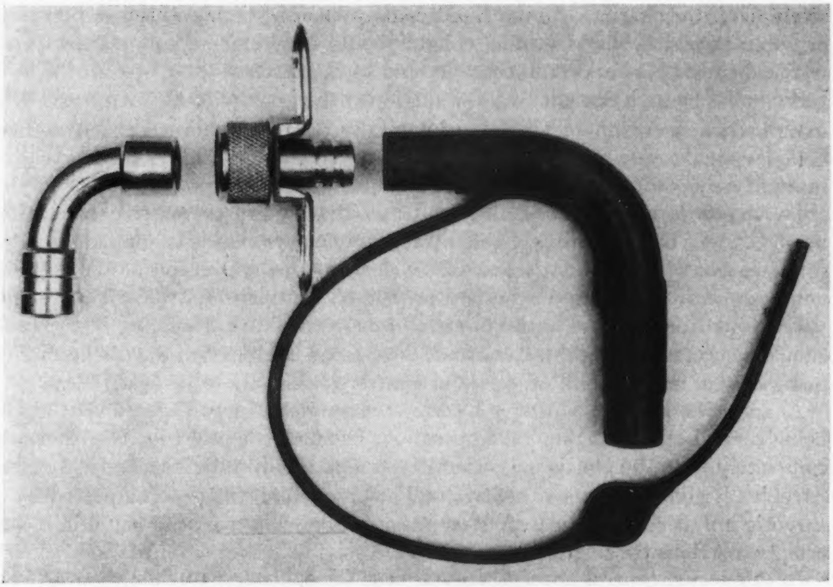


FIGURE 4. Cuffed tracheostomy tubes in one-inch diameter glass tubes, showing cuff with seam inflating eccentrically (left) and even inflation of seamless cuff (right).



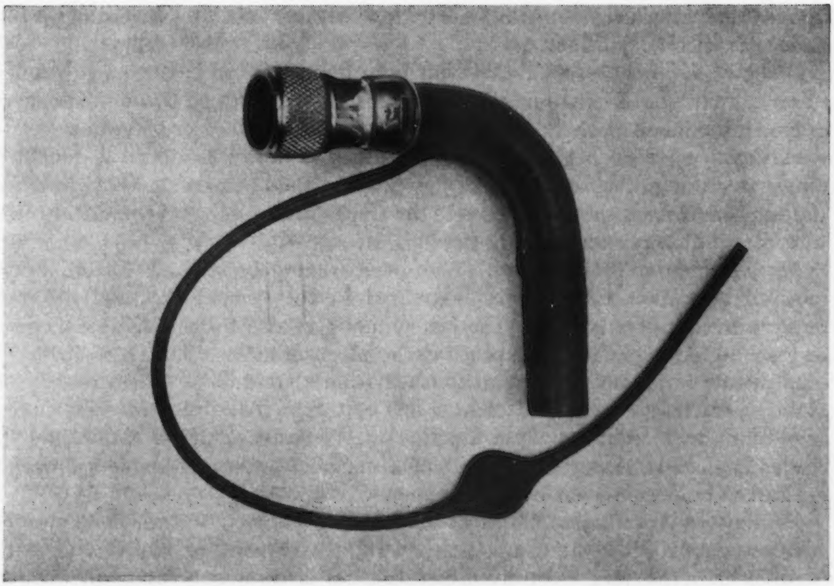


FIGURE 5 and FIGURE 6. Horner Connector (B.O.C. Canada).

To permit the cuff to lie within the trachea, the intratracheal portion is relatively long. In consequence, the tracheostomy must be high and the second ring or space should be divided. The cricoid should be protected by an intact first tracheal ring. It is important that the end of the tracheostomy or endotracheal tube should be high enough to allow suction catheters to pass easily into the left main bronchus. Adequate air entry bilaterally does not indicate that the tube is high enough, only that it is not in the right main bronchus. A further reason for high tracheotomy is that the lower the opening, the nearer the tube is to the great vessels of the neck and the greater is the danger of massive secondary haemorrhage. This is more probable if the origin of the vessels is anomalous (81).

A circular window is cut from the trachea, following division of the thyroid isthmus. Both these manœuvres are performed routinely and have been found valuable not only at the initial insertion but in case early changing of the tube should be necessary. In the latter event, there is less likelihood of the tracheostomy being closed, as though by a series of shutters, when the tube is withdrawn.

As stated above, tracheostomy is performed semi-electively, assisted ventilation being carried out throughout the operation. The endotracheal tube is withdrawn completely from the glottis only when the tracheostomy tube is securely in place. Atropine is given as premedication in all instances and this is accompanied by a narcotic unless contraindicated. Respiratory depression from the narcotic is not usually a serious consideration in patients receiving artificial ventilation.

In this series, general anaesthesia was used for almost all tracheostomies. This varied from 50 per cent nitrous oxide with oxygen and muscle relaxant to sodium thiopentone: nitrous oxide: halothane with or without relaxant, according to the patient's general condition.

Changing Tracheostomy Tubes. It has been found advisable to change rubber tubes more frequently than metal. If tracheostomy is followed by marked oozing of blood, a change after 24–48 hrs. may be required. More usually, however, a weekly change suffices. Until the tracheostomy is firmly established, difficulty may arise during this procedure and two people should be present. One intubates the trachea through the glottis, before the tracheostomy tube is removed. In this way, ventilation is under control throughout.

Complications of Tracheostomy. Those most commonly seen are infection and mucosal ulceration. The former is treated in the normal way and did not prove worrying in this series. The latter may give rise to considerable anxiety and is most likely in patients exposed to the effects of hypotension. Bleeding from tracheal ulceration must be distinguished from that due to other causes, for example, tracheitis sicca. Treatment seems best carried out by use of an uncuffed tube and the Mörch technique. Suction may aggravate the situation and, if tracheitis sicca is suspected, the use of a machine producing sudden powerful expiratory movements has been recommended (82).

Cardiovascular collapse following tracheostomy has been described and various causes suggested (83–85). Among these, sudden reversal of hypercarbia with possible accompanying electrolyte disturbances is commonly accused. Sudden collapse during tracheostomy may relate to vagal overactivity from hypoxia and mechanical stimulus especially when atropine has been omitted.

In the present series, no post-tracheostomy deaths were observed, although hypotension requiring vasopressors for some hours has been seen. This usually followed tracheostomy in patients who had suffered severe hypoxia and it is thought that a resulting reduction in myocardial efficiency was responsible. Electrocardiographic evidence of myocardial ischaemia was observed in several instances.

Bronchoscopy. This has been found to be of very occasional value and may be dangerous. Bronchoscopic equipment should be constantly available and has been found life-saving in two situations: (i) Haemorrhage within the bronchial tree, the combination of blood and secretion forming crusts not removable by suction catheter. (ii) Marked crusting in association with staphylococcal pneumonia. Again, two persons should be present and only very limited periods without ventilatory assistance should be permitted. If the larynx is not of immediate interest, the bronchoscope may be passed through the tracheostomy.

NON-RETURN VALVES (41). Some form of non-rebreathing system is preferable to one providing carbon dioxide absorption, for a number of reasons:

(i) The circuit becomes simpler.

(ii) Soda-lime does not have to be changed.

(iii) Expired gas can be collected and measured.

(iv) Contamination of the machine is less likely.

(v) Expiratory resistance may be lowered.

In practice, non-return valves have certain limitations:

(i) They tend to "leak," so that a portion of the expired gas is rebreathed. This is of little consequence, except in volume measurements. Using such a valve, for example, Flutter-type valve, Reuben Valve, Mörch Valve (78), a meter must be placed between the valve and the patient. In this regard, the Wright Anemometer is particularly useful.

(ii) They render insertion of a negative phase more difficult, although such a phase will increase the efficiency of flutter valves by causing early closure.

(iii) Some of those which close efficiently on expiration, offer a small but significant expiratory resistance at normal flow rates, for example, the Etsen modification of the Fink valve permits collection of expired gases and closes promptly but has an expiratory resistance of 3–5 cm. H_2O at normal flows. However, such a valve may be inserted in a circuit temporarily for purposes of measurement.

Many machines are equipped with non-return systems and mostly belong to the group of intermittently opening reducing valves (see below). Some have a housing around the expiratory valve from which expired gases may be collected.

When the machine is not equipped with a valve, the Mörch non-return valve has been found to be efficient, as has the Beaver flutter valve. These are placed as near to the patient as possible, to minimize dead space. They must be changed at intervals and therefore more than one must be available for each patient. The former is changed and cleaned daily, the latter every two hours. This is necessary because moisture collects on the rubber diaphragm and hampers its free movement.

HUMIDIFIERS. Patients must be adequately hydrated and the respiratory gases must be humidified. Lack of attention to this causes a high incidence of pulmonary

complications. Certain machines are equipped with humidifiers, although the efficiency of these varies. While a high relative humidity is desirable in all patients, actual droplet administration is frequently of value. This is the case in all patients with copious secretions, or in those requiring intrabronchial medication. The droplet size should be 0.5–10 μ (86), which is provided by relatively few pieces of equipment. Larger droplets are inefficient in liquefying sputum and may cause respiratory embarrassment, while smaller droplets are absorbed too quickly. The optimum size is probably 3–5 μ.

Where a machine is to be used which does not have a humidifier, one must be placed in the circuit. One may either deliver the inflation volume over hot water (87) or put a T-piece into the circuit near the patient and deliver droplets from a nebulizer by this means. Alternatively water (not saline) may be delivered from an infusion set through a needle inserted in the inflation tubing. The possibility of tracheostomy infection from humidifiers should be remembered. Meticulous cleanliness is essential.

VENTILATORS. These have been discussed at length in recent publications (41, 88) and vary greatly in design and efficiency. They may be discussed under a variety of headings.

(*a*) *Motive force.* This is either an electrical motor or compressed gas, each having its advantages and disadvantages. The former is relatively reliable, expensive initially and requires to be of a special approved type. The latter is more common, less expensive, and very variable in reliability. Both forms of motive force are subject to failure and each patient should have an alternative method of hand ventilation available at all times. In this regard, the Ambu type resuscitator (89) has proved most useful.

(*b*) *Circuits.* Essentially, these fall into three groups. (i) Pistons or bellows which draw in room air on opening, then, by a series of valves, deliver this to the patient. Both electrical- and gas-operated machines fall into this group. (ii) Motor blowers: essentially, these are intermittently functioning reversed vacuum cleaners. (iii) Intermittently opening reducing valves. These are all compressed-gas-operated machines, functioning by exposing the patient's airway intermittently to a source of compressed air or oxygen. The pressure at which this exposure is made and the rate at which the gas flows is controlled by the machine. These are usually patient triggered but may also be equipped with an automatic sett ng.

Also in this group is the pneophore valve which, by means of a diaphragm mechanism, controls the flow of gases. This latter type of equipment is of limited value for the prolonged treatment of respiratory insufficiency.

(*c*) *Principles of operation.* Machines must have one of two limiting factors to inflation. This is either a preset pressure or volume. Consequently, machines are all either pressure constant-volume variable or volume constant-pressure variable (90). In the first instance, tidal volume will fluctuate inversely with changes in total resistance. In the second, the tidal volume will remain constant while the pressure at which it is delivered varies directly with the resistance. In each instance, this variable factor is limited by the machine's capabilities. For most

purposes, a versatile machine should be capable of delivering over 1000 ml. per stroke and pressures of 50–60 cm. H_2O.

Certain features are essential on all volume-constant machines. (i) They should have a manometer in the circuit, for use as a resistance meter. An increase in pressure suggests the possibility of the need for bronchial aspiration, correction of bronchospasm or left heart failure, or the need for more muscle relaxant in conditions such as tetanus. (ii) They should also possess a safety valve so that a lung will not be ruptured, if the resistance rises precipitously, the machine inexorably delivering its preset volume. The Mörch respirator (78) has been found to be a very reliable, if not versatile, machine. Being intended for use with an uncuffed tube, it possesses neither safety valve nor manometer. The humidifier has been found inefficient and, in consequence, the following modification has been introduced and found to be a great improvement. The humidifier cylinder was removed and, in its place, a one-inch diameter threaded tube was inserted. To this was attached the delivery tube to a separate humidifier. An anaeroid manometer and a blow-off valve (loaded at 50 cm. H_2O) were tapped into the top of the one inch tubing.

(*d*) *Respiratory wave form*. Opinions differ as to the optimum wave form. Certain machines apply I.P.P. to the upper airway in a preset wave form while, in others, the duration of each phase and the shape of the pressure curve produced may be adjusted. The sinusoidal curve has been strongly advocated as that likely to effect cardiac output least. However, a square wave is held by many to give the greatest inflation in the shortest time. The square wave is produced by machines delivering high gas flows from the start (e.g. 100–200 L./min.). Maximum pressure is reached rapidly in the upper airway (giving a vertical up-stroke to the inflation curve). Ventilation is then largely dependent upon the duration of application of this pressure (giving a horizontal component to the curve). The potential disadvantage of such wave form might be that in patients with low compliance ventilation would only be achieved at the expense of venous return.

If a severe distribution defect necessitates slow inflation or some expiratory retard is utilized to prevent trapping, the vertical components of the wave form will be impracticable and a sinusoidal curve more desirable. Again, venous return will be impeded.

Inflation. During this phase, tidal volume will be determined. Air should be delivered at a flow of at least 40–60 L. per min., and it should be possible to achieve this fairly rapidly. The intermittently opening reducing valve type of machine usually delivers gas at over 100 L. per min. and at least one is capable of flows up to 200 L. per min.

This phase is adjustable on many machines and should be as fast as is compatible with adequate ventilation, distribution and comfort. Patients with pain in the chest object to machines reaching maximum inflation pressures extremely rapidly.

Expiration and Pause. These two phases together should be at least as long as inspiration and preferably longer to permit adequate venous return (29). Expiration itself should be as rapid as possible except in patients with air trapping.

In the latter, a small resistance in the first part of expiration may diminish trapping. Again, phase adjustability and an adjustable expiratory retard may be of value.

Negative Phase. This has been shown to be of value in hypovolaemia (30) and in patients with low lung volumes (91). The danger of accentuating trapping in emphysema has been suggested (92) and no improvement in ventilation has been demonstrated using a negative phase in a small series of such patients (25). It may be most valuable when inserted at the end of the expiratory phase (93).

(*e*) *Patient-triggering mechanism.* Certain machines possess a mechanism whereby each respiratory cycle is initiated by the patient creating a small negative pressure in the circuit. This may be fixed to work at, say, -2 cm. H_2O or may be variable. Most machines with such a device can also be set to work automatically. Frequently, the automatic control may be set at a slower rate than that of the patient so that, should he fail to trip the machine, it will then cut in on its own. While this mechanism is not essential, it has been used very frequently in the present series and has been most helpful. The patient triggering mechanism is contraindicated in the treatment of stove-in-chest, until the weaning phase is reached. Clearly, it will be inappropriate in the presence of apnoea.

(*f*) *Machines of use in both operating room and respiratory insufficiency.* Certain machines are designed in such a way that they may be used either in the operating room or in the treatment of respiratory insufficiency. Although such versatility usually leads to compromise, the concept is most appealing to the smaller hospital. The essential differences between the two types of ventilator are these:

(1) A machine for use in anaesthesia must have a circuit, separate from the motive force, into which one may introduce anaesthetic gases. Several machines, designed for anaesthesia and possessing such a circuit, can be modified for I.P.P. therapy by opening an air intake valve. Thus, as the bellows expands, instead of anaesthetic agents filling it, air is drawn in. As the bellows empties, the air valve closes and the air is delivered to the patient. Under such circumstances, the machine must obviously be used with a humidifier and non-return valve. When used for anaesthesia, these are removed and the machine substituted for the rebreathing bag of an ordinary anaesthetic circuit, with its own circle system, to and fro absorption, or non-return valve.

Clearly, such interchangeability is not possible with the intermittently opening reducing valve type of respirator. However, they may be adapted for use in anaesthesia (as may the bellows or piston type not designed for this purpose) by placing the rebreathing bag of the anaesthetic circuit in an airtight container and applying I.P.P. to the space between bag and container (94). Such a machine has now been made available commercially.

(2) Machines for use in operating rooms must be explosion-proof, rendering those which are gas-operated most frequently acceptable.

(3) Machines used in operating rooms may be relatively complex, but satisfactory under the continual observation of a physician. Such a machine may be difficult for the inexperienced nurse to understand.

(4) Machines for respiratory insufficiency require a humidifier and non-return valve. (See above.)

(5) Machines used in treating respiratory insufficiency may be in use for weeks on end; after anything more than the few hours customary for anaesthesia, minor imperfections of pressure wave form, expiratory resistance, and long-term reliability become of increasing importance.

(*g*) *Alternative methods of ventilation.* Emergency equipment, with which to ventilate any patient whose ventilator ceases to function satisfactorily for any reason, must always be available. Attendants should all know how to use this and, in cases of emergency, must do so until help is obtained.

(*h*) *I.P.P. in children.* As mentioned above, a given volume of air will be delivered at a specific pressure regardless of the age of the patient, the only exception being neonates. Thus I.P.P. equipment for children will require only slightly lower pressure ranges than those of adults. However, considerations of volume and rate will be very much more critical. Bearing in mind that a 7-lb. infant may have a tidal volume of 20 cc., it is obvious that dead space must be minimal. Similarly, an infant's respiratory rate may require a ventilator to function as fast as 40 per min.

Clinical Management

The sections that follow will be concerned with the clinical application of the above principles, without any discussion of first aid.

Patients requiring assisted respiration present in two ways: the first is the patient who needs respiratory assistance at once; the second is the patient whose ventilation fails gradually while he is under observation.

The first group needs emergency treatment. An airway is established and ventilation started as previously described. In an acute emergency of this type, measures to secure these ends take precedence over all other considerations. When they are secured, a complete history can be obtained, physical examination carried out, and other emergencies dealt with.

History taking and examination will have been done, of course, in the case of the patient with respiratory failure of gradual onset, but the following investigations are important: chest X-ray, Hgb., WBC and differential, complete urine examination, serum electrolytes and NPN, ECG examination, culture of the bronchial secretions, and measurement of ventilation. If facilities exist, the arterial pH, pCO_2, and CO_2 content should be determined before the institution of artificial respiration and an hour or so after it has begun.

In general, the use of I.P.P. does not alter the management of most conditions in which it may be needed but a few points merit special emphasis. Successful treatment depends upon attention to detail and this must be impressed upon all who deal with these patients. This is the only way in which minor deviations from normal can be prevented from turning into major catastrophes and this responsibility falls in the first place upon the nurses.

Nursing care. The successful use of assisted ventilation depends upon the skill

of the nurses, who should therefore be specialists. In practice, several months' experience are needed to acquire the necessary skill and confidence. The nursing problems are those associated with the nursing of very sick patients, the use and the understanding of the specialized equipment, and the recognition and management of a developing emergency.

Apart from general nursing care, the following are the routines in use in the Respiratory Unit at the Toronto General Hospital in acute cases: half-hourly observation of heart rate, blood pressure, respiratory rate, and airway pressure; half-hourly tracheal toilet—or more frequently if necessary—and note taken of quantity, consistency, and colour of the aspirate. The humidifier must always be kept full. In some patients, half-hourly or hourly record of the ventilation is made. Every two hours, the patient is turned and the cuff on the tracheostomy tube is deflated for two minutes and then reinflated; there is no good evidence that this is necessary to prevent ischaemic ulceration of the trachea but it is done in the hope that it will. The patient's temperature is recorded every four hours and the fluid balance every eight.

The large number and variety of nursing problems that arise in these patients will become apparent in the sections that follow. The outline given above refers to the acute case. As the patient improves, the various observations may be made less often and the frequency of suctioning is adjusted to the amount of secretions present.

The care of the chest. The problems in the chest are the prevention of atelectasis and of infection. These arise because the natural barriers to and humidification of the respiratory tract are bypassed and because effective coughing is abolished. The presence of a foreign body, the tracheostomy tube, in the trachea promotes the formation of secretions and, particularly in asthmatics, tends initially to aggravate spasm of the bronchi. In a few patients, the bronchial and tracheal mucosa is destroyed by infection.

Bronchial secretions are removed by catheter suction. They are brought within reach of the catheter by physiotherapy to the chest. The value of chest physiotherapy, that is of percussion and squeezing of the chest wall, has been emphasized by many writers (95, 96). All patients in the Toronto General Hospital Respiratory Unit, except those with stove-in-chest or in shock, are given physiotherapy twice daily by members of the department of Physical Medicine. It is useful for the nurses to have some knowledge of chest physiotherapy.

Suctioning is done with sterile coudé rubber catheters, size 16 or 18, which are used once and then resterilized. These catheters are of soft rubber, hollow to the end. The hole is about 1 cm. from the end. Straight catheters enter the right bronchial tree on the vast majority of occasions (97).

The catheter is connected to the suction machine via a y-piece, one limb of which is open to room air. The machine is turned on and the catheter inserted with the tip pointing to right or left, depending upon which main bronchus is to be aspirated. It is gently insinuated as far as it will go. A finger is then placed over the limb of the "y" and the catheter gently withdrawn with a slight twisting movement. The procedure is repeated until all reachable secretion has been aspirated from both sides. While this is done, the patient must be disconnected

from the ventilator. To prevent hypoxia, it is a safe rule for the inexperienced nurse to hold her breath from the moment that she disconnects the ventilator and then reconnect it when she has to take a breath herself.

To maintain secretions fluid enough to be aspirated, the inspired gases must be properly humidified, but the most perfect humidification of the inspired air will be useless if the patient is dehydrated. The avoidance of dehydration is the essential factor in maintaining fluid bronchial secretions. Once hydration is achieved, humidification is relatively simple.

The use of these techniques will prevent the occurrence of serious intrathoracic complications in almost all patients who present without intrathoracic abnormality and will control these complications in those who present with a "wet chest." They will also render bronchoscopy a rare event.

The management of infection and other intrathoracic complications in these patients is the same as in any other circumstances. Occasionally, unusual organisms will be found in the bronchial aspirate, for example *B. Pyocyaneus.* We have not seen such organisms cause any serious pulmonary or bronchial infection nor to persist in the bronchial secretions once the tracheotomy tube is removed, although rarely they are capable of causing serious pulmonary infection.

The Cardiovascular System. Congestive cardiac failure is recognized and treated in the usual way. It is not a contraindication to the use of I.P.P. which may, by providing adequate ventilation, relieve it.

Shock and hypovolemic states are particularly dangerous because many of these patients have cardiac disorders of various types—myocarditis, trauma, arteriosclerotic heart disease, previous ischaemia of myocardium due to anoxia—rendering them liable to cardiac arrest from hypoxia. Further, I.P.P. aggravates the circulatory difficulties present in hypovolaemia, endangering renal function and exposing the patient to the risk of anoxic encephalopathy. Such states are dealt with in the usual ways, by vasopressors, blood transfusion, and arrest of haemorrhage. The use of a negative phase has been discussed above.

Pulmonary oedema may be the cause of a gradual or acute change in the otherwise satisfactory progress of many patients. It may be detected clinically and by a fall in tidal volume, with pressure constant machines, or by a rise in pressure with volume constant machines. It may occur in any elderly patient secondary to a change in cardiac rhythm or in any post-thoracotomy or stove-in-chest patient from either atrial fibrillation or actual myocardial damage. Methods of management are not altered by I.P.P. which may in fact be advantageous. "Pulmonary oedema" has also been seen in the course of treating severe emphysema and this is discussed separately under that heading.

The Nervous System. The state of sensory deprivation (98, 99) occurs in these patients, particularly in those in whom there is interruption of the sensory pathway; it occurs less often in patients treated with I.P.P. than in those treated in tank respirators. Confusional states and deliria are not uncommon and when they occur some sort of restraint is usually necessary to prevent the patient interfering with the ventilator.

Anxiety and fear are inevitable in any conscious patient who needs artificial respiration and should be treated with full doses of appropriate drugs. The main

factor limiting choice, dose, and routes of administration of drugs is their liability to produce hypotension. Meperidine is a frequent offender. Other factors are their liability to constipate and to cause addiction.

The care of paralysed limbs and the prevention of "trophic" lesions are important parts of the nursing routine. In the prevention of bedsores a "ripple mattress" is helpful but does not obviate the need for careful attention to pressure points and frequent turning of the patient. The care of the eyes may be overlooked in paralysed patients and in those who are unconscious for a long time. All such patients should be given antiseptic eye ointment prophylactically and if there is any facial weakness or any injection of the conjunctiva, an ophthalmic consultation should be sought at once. A tarsorrhaphy is quick and easy to do and undo, and will prevent disastrous ocular lesions.

Diet. Many patients are unable to swallow as a result of bulbar palsy, pseudobulbar palsy, or disturbance of consciousness, and many others need gastric or duodenal suction. Hence a duodenal tube is often needed for shorter or longer periods. Gastrostomy may be needed for oesophagitis or because of persistent bulbar palsy.

In the absence of dysphagia, patients should have a normal diet or a diet appropriate to their condition. If they need tube feeding, the diet must contain sufficient fluid, calories, vitamins, and minerals. An effective method is to homogenise a normal day's diet in a mechanical blender and to adjust its volume to provide 1 calorie/ml. This mixture is a fluid of unappetising appearance, high viscosity, and low salt content. Diluted appropriately, this has proved entirely satisfactory. The low salt content is an advantage rather than otherwise, as no special mixture is needed for patients with cardiac failure. Salt may be added as required for other patients.

Fluid Balance. In the adult a daily (24 hrs.) intake of 3 L. is satisfactory but this volume may need to be altered according to the circumstances of any given case. Unless the volume and type of fluid ingested are charted, it is easy for these patients to become deficient, leading to drying of bronchial secretions and to electrolyte disturbances. The setting of ventilatory volumes is not exact and some overventilation is permissible in virtue of renal compensation. This margin is reduced by electrolyte disturbances. This is particularly important if ventilators without a patient-triggering device are used. Other frequently occurring complications that may be mentioned under this heading are paralytic ileus and constipation. They are managed in the usual ways.

Urinary Tract. Retention of urine is a common event and may need treatment by indwelling catheter. It is particularly important to avoid infection or to control it promptly. Two among many reasons may be emphasized: first, because such infections are commonly due to gram-negative organisms and gram-negative septicaemia is a potent cause of hypotension and, second, because of the danger of calculus formation in the renal calyces in those who are recumbent for long periods. Large volumes of urine are an aditional protection against both infection and calculus formation. A further protection, in paralysed patients, is to nurse them on a rocking bed as soon as this is possible.

The Use of Drugs. In general, the use of drugs is not in any way affected by artificial ventilation. A few points are worth special mention.

Sedatives can be used in full dosage without fear of interfering with ventilation by depression of the respiratory centre. In most of these patients, they should be used in sufficient dosage to induce amnesia for the acute stages of the illness and this should be explained to the patient's relatives. The main contra-indication to this use of drugs is the presence or danger of hypotension.

Drugs may be used in these patients in unusual ways and cause unexpected results. The best example of this is the use of nitrous oxide continuously for days on end in the treatment of tetanus and the production of agranulocytosis (100).

Muscle relaxants may be of great value and, provided that skilful nursing is available, there is no great danger in their use. There are two main indications for the use of relaxants: first, to abolish the convulsions of tetanus or status epilepticus, and second, to remove other causes of interference with artificial respiration. Tetanus and status epilepticus will be considered below and only muscular interference of other origin will be considered here.

Such interference occurs to some extent in all patients for a short while when assisted ventilation is begun. Most patients adapt themselves easily and quickly to the rhythm of the respirator provided that attention has been paid to minimizing the irritation of the tracheostomy tube and that sedation is adequate. A few do not and their resistance to the ventilator may be such that it is impossible to overventilate them and reduce their stimulus to breathe. If this situation cannot be quickly controlled by simpler methods, then relaxants will permit the establishment of adequate ventilation and allow time for the patient to adapt himself to the situation.

A suggested indication is to remove part of the resistance to ventilation, not on account of the inability of the patient to co-operate but to reduce the pressure required to secure adequate ventilation. This situation arises in patients with some intrathoracic abnormality, of which by far the commonest is emphysema with or without bronchospasm, pneumonia, and excessive amounts of bronchial secretion. In these patients, the increased physiological dead space may require large tidal volumes. To secure these, high pressures and slow inspiratory flow are often needed, the mean intrathoracic pressure is therefore raised and the cardiac output may be reduced. It has been suggested that the elimination of the muscular component of the thoracic wall resistance to ventilation may enable the pressure to be reduced to levels that do not embarrass the circulation. There is evidence to suggest that relaxants will lower total resistance to inflation, possibly by abdominal relaxation. This indication must be regarded as still *sub judice*.

A third small group of patients in whom relaxants are useful are those with gross tachypnoea and consequent low tidal volumes. This is usually associated with pneumonia, occasionally with trauma to the chest and lungs. These conditions in themselves interfere with ventilation but the larger factor demanding respiratory assistance is exhaustion by the labour of inefficient respiration. In this group of patients, if narcotics prove ineffective or are contraindicated, the use of relaxants may have to be prolonged until the lesions stimulating the tachypnoea have resolved sufficiently to permit adequate ventilation without paralysis.

There is a final group of patients in whom relaxants may be useful. They are patients in whom adequate ventilation can only be achieved by assisted respira-

tion but in whom adequate ventilation also permits them to be restless. This may occur in any condition of which a confusional state is a complication. Most such cases can be controlled by skilled nursing and sedation but, in some, sedation may be contraindicated and relaxants may be necessary to secure ventilation.

The choice of relaxant depends upon the probable time for which it will be needed and the undesirability of combining depolarising agents with competitive inhibitors. Both types of relaxant have been used for long and short-term cases. In general it is our practice to use short-acting compounds to establish artificial ventilation and longer-acting compounds (laudexium) for other purposes. If succinylcholine is used for long periods, the concentration must be adjusted to avoid over-hydration; it is most conveniently given in a 1:500 solution. The rate at which this is infused may be altered to provide a required degree of paralysis. When prescribing relaxants for administration by nurses, no attempt has been made, with the exception of tetanus, to adjust the dose to the patient's response. A regular intramuscular dose has been ordered and any excess will be of little consequence during artificial respiration. Accumulation may occur; paralysis persisted for 24 hrs. beyond the last dose of laudexium in one instance. At that time, prostigmine was effective. The dosage of laudexium is 30–60 mg. intravenously to induce paralysis and 12 mg. intramuscularly repeated as often as necessary (e.g., every 2 hrs.).

The decision to use relaxants is not to be taken lightly. It introduces the complication of total paralysis into an already hazardous situation and interferes with physical examination. It should be remembered that auditory acuity is unaltered or enhanced during such states (101).

A last point in connection with the use of relaxants is one of diagnosis. As the effect of relaxants wears off and the patient starts to move, the first feeble movements are poorly co-ordinated and we have seen these diagnosed as almost any sort of involuntary movement from epilepsy to clonus.

The Restoration of Spontaneous Ventilation. Patients who have required I.P.P. for a few hours after taking a large dose of short-acting barbiturate present little difficulty. Their ventilation is easily measured and when it is adequate the respirator is disconnected in exactly the same way as the anaesthetist ceases to ventilate a patient after an operation.

In those who have needed I.P.P. for longer periods, two problems arise. The first is the patient's ventilatory ability, the second is psychological dependence on the respirator. The latter is dealt with by explanation, reassurance, and by permitting spontaneous ventilation initially for brief periods only. The most important measures are to wean the patient from the respirator only when his ventilatory ability is adequate and to ensure that the patient knows that the respirator can be reconnected at any moment.

The ventilatory measurements of most value are the tidal volume, respiratory rate, and vital capacity. They are more informative if recorded on a spirometer than as number of ml., and have two purposes. The first is to determine whether the minute volume and tidal volume are adequate at the moment and the second is to determine the ventilatory reserve. This term is used to mean the difference between the tidal volume and the vital capacity. The latter is, of course, of

limited significance, but it is easy to do and imposes little effort on the patient. Serial observations are essential.

In the patient without muscular weakness, the factors precipitating respiratory failure, for example, excessive bronchial secretions, have been controlled, atelectasis, ileus, and pneumonic consolidation have been corrected, and the application of the principles set out above is then quite straight-forward. The problem is fundamentally to prevent a relapse, whether cardiac or respiratory.

In the patient recovering from paralysis, additional problems arise. Every physician who has looked after cases of poliomyelitis with respiratory paralysis is familiar with the danger of sudden death in these patients. This is likely to occur when they have been free of the respirator and apparently stable for some days or longer. The cause of death is unexplained but is probably sudden failure of the respiratory muscles. Because such fatigue is rapid (102), measurement of ventilatory volumes offers poor protection. Consequently, respiratory assistance must not be withdrawn too early. One very satisfactory method is gradually to transfer the patient from a respirator to a rocking bed (103) as the first step in his convalescence. As the vital capacity improves, the rocking bed may be turned off for gradually increasing periods. During these periods, the position of the patient should not hamper his ventilation. Thus a patient with diaphragmatic weakness should never be placed head-down unless he is being ventilated, whereas a patient with good diaphragmatic movement and weak intercostal and abdominal muscles is often better able to ventilate if he is placed slightly head-down, rather than strictly horizontal (104).

Rough guides, in adult patients, are that a vital capacity of 300–400 ml. will allow a patient to use a rocking bed but will not enable him to dispense with a respirator for long. A vital capacity of 400–600 ml. allows useful spontaneous ventilation for short periods and patients with vital capacities of 800 ml. and over usually do not need assistance unless some intrathoracic disorder occurs.

In the sections that follow, some of the main points in the management of the various groups, classified by diagnosis, (Table I) will be discussed.

Management of Neurological Disorders

With the exception of tetanus, patients with diseases in this group present little difficulty in the management of assisted ventilation. The general principles outlined previously apply.

Drug Intoxication. Of the patients with respiratory insufficiency resulting from affection of the central nervous system, the largest group were those with barbiturate intoxication (Table I). These are the simplest group to manage and the principles and details are well recognized. The general opinion is that, provided a patient is not moribund when first seen, it is almost always possible to save his life. The essential points are the airway, adequate ventilation, the correction of hypotension, the regulation of fluid and electrolytes, and other features of the care of the unconscious patient (105, 106). The main variables are the age and clinical state of the patient before ingestion of drugs and the nature and dose of the drug ingested. Once the airway is secure and adequate ventilation is established, the most urgent problem is to correct hypotension. Gastric lavage should

not be performed and, if practicable, stimulants should not be given until the airway is protected by a cuffed endotracheal tube, lest aspiration of gastric contents should occur. Blood transfusion and infusion of plasma are sometimes recommended to restore satisfactory blood pressure. It must be very rare that simpler measures such as pressor agents fail.

Lower Motor Neurone Lesions. This group includes poliomyelitis, polyneuritis, myasthenia gravis, certain metabolic disorders such as hypo- and hyper-potassaemia, and certain muscular disorders, particularly polymyositis.

Underventilation may be caused by airway obstruction due to bulbar palsy, by weakness of the respiratory muscles, or, rarely, in poliomyelitis by damage to the medullary centres. Atelectasis, pneumonia, and pulmonary oedema may aggravate any such respiratory embarrassment and are particularly likely to occur if there has been any delay in the recognition and institution of proper treatment of bulbar palsy.

The clinical diagnosis of both bulbar palsy and respiratory impairment (107) have been widely discussed in the recent literature and will not be considered in detail here. Respiratory failure is not of abrupt onset in these conditions. The clinical problem is to assess the extent to which ventilatory function is affected, to follow its changes by serial observations, and to institute appropriate treatment in good time. Respiratory insufficiency, as judged by alterations in pCO_2, is not present until 80 or 90 per cent of the ventilatory function is destroyed. Hence, arterial pCO_2 levels will be of no value and if anxiety has led to overbreathing, the pCO_2 may be low when the ventilatory reserve is already greatly diminished. The most convenient method in practice is to measure the vital capacity twice daily or more often if necessary. If appropriate apparatus is not available, a useful rough guide to the vital capacity is to ask the patient to count aloud, at the rate of two digits a second, as high as he can in one breath. Ten digits is approximately equivalent to a vital capacity of 1 L. More elaborate methods of investigating respiratory function are often either impossible or contraindicated.

In very general terms, if the vital capacity is less than 50 per cent of the predicted normal, a respirator should be available and if less than 30 per cent of the predicted normal it is likely to be needed. In cases of poliomyelitis, to avoid fatigue of the respiratory muscles, it should be used when the vital capacity is less than 30 per cent of the predicted normal.

Bulbar palsy and the consequent accumulation of pharyngeal secretions may be dealt with, if isolated, by postural drainage. This is easier to manage in children than in adults. It should not be attempted if there is any diaphragmatic weakness lest the additional work required of the respiratory muscles lead to sudden respiratory failure. Paralytic ileus and severe pain in poliomyelitis and polyneuritis often make it impossible to impose on the patient the additional discomforts of lying prone or head-down and a cuffed tracheostomy tube will frequently be preferred.

The problems of respiratory insufficiency due to paralysis are more complicated in myasthenia gravis. The paralysis is variable and may change rapidly. Sudden fatigue of the respiratory muscles is the probable cause of the sudden death that is notorious in this condition (108). Secretions are apt to be more profuse as a

result of anticholinesterase therapy, which may also cause respiratory paralysis. These factors are present in any case of moderately severe myasthenia gravis and are aggravated by the hazards of sternotomy after thymectomy. These can be reduced if a tracheotomy is done, through a separate incision, at the time of thymectomy; and if anticholinesterases are withheld in the immediate post-operative period. Respiratory insufficiency can then be easily handled by the respirator and the correct dose of anticholinesterases re-established in the usual way. This method of managing the severe case of myasthenia gravis undergoing thymectomy is satisfactory, but it demands experience of the illness, of post-operative management, and of I.P.P.

Spinal Cord Lesions. The consequences to respiratory function of spinal cord lesions depend on the situation of the lesion. If the segments giving rise to the phrenic nerve, usually C3, 4, 5, are damaged, then inspiration, expiration, and coughing will be impaired. If the lesion spares these segments or roots, then only active expiration and coughing will be affected. In the latter case, the expiratory reserve volume is diminished; in the former, inspiratory reserve volume is diminished also.

Clinically, therefore, the consequences are a liability to retention of bronchial secretions, atelectasis, and pneumonitis in all cases, as well as underventilation in some. The possibility of underventilation is increased by the frequent occurrence of paralytic ileus. In the later stages, the situation is sometimes complicated by spasticity of the trunk muscles.

Most of the patients whom we have seen with respiratory insufficiency due to cervical cord lesions are cases of injury often complicated by chest (*vide infra*) and head injuries, both of which may hamper respiration still further. The situation under these circumstances needs very careful neurological, surgical, and respiratory supervision.

A final diagnostic point is the occurrence of minor cervical cord injuries in patients whose major injury is to some other part, usually the head, sometimes the chest (109). In many cases these injuries to the cord occur in patients with cervical spondylosis (110) and a characteristic feature, not always present, is the presence of spasticity in the acute phase. This injury may account for respiratory embarrassment which is otherwise difficult to explain.

The injured neck is most conveniently immobilized by ice-tong traction or, in cases of minor injury, by placing the head between sand bags.

Tetanus. In Western Europe and North America, tetanus is a relatively rare disease and large series come mostly from lands with less lavish medical facilities in which the use of modern methods of assisted respiration are not widely available. The use of relaxants and artificial respiration in tetanus is an innovation in treatment and has been of widespread interest (111–114). Their place is by no means established.

The theory is that tetanus is a self-limited disease and, if it is not fatal, the patient will make a complete recovery. This view is not altogether certain in very severe cases and there is evidence to suggest that sometimes tetanus is "inevitably" fatal. Secondly, in a very large series, over many years, there has been a steady fall in the mortality not related to any particular treatment. Thirdly, other

methods of treatment are very effective (115). In seven years at the Toronto General Hospital, there have been ten cases with one death. This was in a very unpromising therapeutic prospect, who died of staphylococcal septicaemia, but was the only case treated by relaxants and I.P.P.

The place of relaxants and I.P.P. is therefore with only the most severe cases, but in some of them it may be lifesaving. The indications for its use are not clear (116). One group took as an indication the occurrence of a spasm that stopped ventilation.

The situation is complicated by a number of factors, the first of which is that little is known of ventilatory function in tetanus. Partial laryngeal obstruction due to spasm, aggravated by efforts to swallow or speak, is common, and it is the usual practice to do a tracheostomy in any case of generalized tetanus. Another important factor is that inspiration produces reflex spasm of the expiratory muscles and, hence, shallow respirations. Another is that the spasm of muscles increased the need for oxygen. The dangers of underventilation are great, particularly as a cardiopathy similar to that of diphtheria has been reported in severe cases of tetanus.

The most satisfactory regimen in a case of generalized tetanus may prove to be early tracheostomy, a constantly maintained level of sedation and a fine adjustment, so to speak, with shortacting intravenous barbiturates, phenothiazines, or meprobamate (117–120). This requires the almost constant presence of a physician. If it proves impossible to control the spasms and allow adequate spontaneous respiration by these means, then relaxants and I.P.P. should be used.

Relaxants or sedation may be needed continuously for three weeks. The appropriate daily dosages vary but are remarkably constant in any one patient. There is, in any patient receiving I.P.P., some variability in the resistance to ventilation, depending on the accumulation and removal of bronchial secretions, on changes of posture, and on residual muscular power. These do not in the usual case cause very much difficulty. In tetanus, as the effect of relaxants wanes, there may be considerable alterations in resistance and extra vigilance is needed to ensure that correct tidal and minute volumes are achieved. This is, therefore, an excellent indication for a volume-constant ventilator; changes in pressure are then taken to indicate the need for suction or for change in relaxant dosage.

In emphasizing the uncertainties and difficulties in the use of this method of treating tetanus, it should not be overlooked that there are a number of advantages. Spasms are abolished, sedation can be lighter, and there is less danger of extreme hypotension and hypoxia. The nursing care of the patient is easier because the same urgency does not attach to reducing the number of stimuli received by the patient. With well-trained nurses, the constant attendance of a physician is not needed.

Management of Emphysema

Underventilation associated with emphysema is, in our experience, most difficult to manage. The problems are those of complex and incompletely understood alterations of pulmonary physiology associated with extensive destruction of lung.

These patients frequently present with severe respiratory insufficiency as a result of a complicating factor, usually infection, but occasionally the incautious use of opiates or oxygen, or myocardial ischaemia.

A proportion of these patients may be returned to a contented life by careful treatment—rest in bed, nursing, antibiotics, steroids, bronchodilators, digitalis, diuretics—and assisted ventilation provides the opportunity to attempt this. In any particular case, prognosis is most difficult. It will depend, to a large extent, upon the relative importance of the basic pulmonary pathology and of the complicating factors. Thus, a knowledge of the detailed history will be most valuable.

The table shows our experience with 23 cases, 8 of whom died. The average length of stay was 24 days and assisted respiration was required for an average time of two weeks. None was admitted until less drastic therapy had been unsuccessful and, in this regard, the use of Nikethamide continuously rather than I.P.P. is of great interest.

The complex problems involved in these cases may be summarized thus:

(*a*) *Carbon dioxide retention.* These patients are frequently accustomed to high arterial CO_2 tensions in the range of 45–60 mm. Hg. Additional acute CO_2 retention may raise the level to 110 mm. Hg. or more. Neither disorder of consciousness nor any other clinical sign has been found to correlate well with levels of arterial CO_2 but disorientation is usual at levels over 90 mm. Hg.

(*b*) *Hypoxia.* Although much attention has been given to the effects of CO_2 retention in emphysema, the commonly associated hypoxia deserves equal or greater respect. The relative degree of hypoxia or hypercarbia varies from case to case and oxygen administration must be carefully controlled, to avoid further CO_2 retention, if respiration is not assisted.

When underventilation occurs, hypoxia may cause cerebral dysfunction, myocardial ischaemia with hypotension and subsequent ECG changes, renal ischaemia with oliguria, and, possibly, gastro-intestinal ischaemia as shown by paralytic ileus and gastric dilatation. In the acute phases, it has been considered advisable to assist respiration with 100 per cent O_2. Once ventilation has been established satisfactorily, 40 per cent oxygen is used, this being the minimum delivered by the intermittently opening reducing valve type of machine commonly used in the management of these cases. I.P.P. by tracheotomy is one of the few ways in which 100 per cent O_2 may be delivered to the alveoli and the dangers of oxygen intoxication must be remembered.

(*c*) *Cardiac failure.* Emphysema progressing to the stage requiring ventilatory assistance is very frequently associated with right heart failure and fluid retention (121). This appears to be secondary to the inability of the myocardium to overcome a raised pulmonary vascular resistance. It has been noticeable that failure resistant to routine therapy may reverse within a very few days, once respiratory assistance is initiated. It is assumed that this is related predominantly to an improved arterial oxygen tension, producing a reduced pulmonary vascular resistance and increased myocardial efficiency.

In the present series, left heart failure has been seen following myocardial infarction, with pulmonary congestion sufficient to produce respiratory insuf-

ficiency in an emphysematous patient. A small group of cases have simulated left heart failure terminally. The pattern in this last group has been as follows: a patient with severe emphysema has developed acute respiratory insufficiency—usually associated with hypotension, hypoxia, and depression of level of consciousness. With vigorous ventilatory treatment, the arterial pCO_2 has been reduced, and the level of consciousness, colour, and general condition markedly improved. After two or three days of such progress, hypotension and fine crepitations have appeared. Death has resulted. At autopsy, the picture has been obscure but most closely resembles the effects of experimental oxygen toxicity. The lungs have been grossly congested and microscopically the alveoli have contained red blood cells. Pulmonary oedema was not present. The alveoli have undergone "foetalization," that is, have become lined with cuboidal epithelium. It is felt that the last finding relates to the 100 per cent oxygen given to these patients for the preceding few days. While the congestion may also be the result of oxygen toxicity, other possibilities are left heart failure, possibly due to a previously anoxic left ventricular myocardium suddenly being presented with a much elevated input, resulting from the improved ventilation and oxygenation, or to trauma from I.P.P. on abnormal lungs.

(*d*) *Neurological accompaniments*. The neurological symptoms which may be associated with chronic respiratory disease are disorders of consciousness, papilloedema, headache, involuntary movements, and rigidity. No characteristic neuropathological findings have been established. The genesis of these symptoms is not certain, but as well as CO_2 narcosis and hypoxia, ammonia intoxication has been suggested. The most common symptoms in our experience have been disorders of consciousness and of behaviour, which do not differ from similar disorders seen in other encephalopathies. Variable rigidity is a usual accompaniment of these symptoms. Involuntary movements, most frequently twitching of muscles on maintaining a posture, have been common. In some patients, the typical movements of asterixis have been present and as the patient improves the twitching is all that remains of this. Occasionally, we have observed gross clonic movements similar to the myoclonic jerks of epileptics and have taken this to be an indication to use anticonvulsants. Papilloedema has been the rarest of the neurological signs.

With correction of the ventilatory defect, the neurological signs improve, papilloedema and the disorder of consciousness disappear although it may take some months for the latter to do so completely. The usual complaint, in those in whom it does not clear up and in whom spontaneous ventilation is adequate, is that they are difficult and touchy. We have not seen any gross social incapacity from persisting confusion, defects of memory, or dementia. Similarly, the involuntary movements have improved. Although minor degrees of twitching may still be present on formal examination, they are not then a symptom of which complaint is made.

The *ventilatory requirements* are a high tidal volume, to overcome the dead space, delivered slowly enough not to exaggerate the distribution defect, and a long expiratory phase to permit maximum emptying and to produce a low mean intrathoracic pressure. Clearly, the higher the tidal volume the longer the expira-

tory phase that will be required. In one small series a negative phase did not prove of value (25) and the danger of this phase aggravating trapping has been pointed out (92). In practice, one is frequently hard put to produce adequate ventilation. One requires a machine with wide phase adjustability and, measuring ventilation continuously, phases and volumes are adjusted to produce maximum ventilation with minimal trapping. This can be detected simply: (i) expiration is observed on the gas meter and if inflation starts while expired gas is still flowing, trapping is occurring and must be corrected. (ii) This may be confirmed by ausculation of the chest. A needle may be placed in the external jugular vein and connected to tubing filled with heparin and saline. Venous pressure may then be observed continuously and the ventilation adjusted to produce the lowest level possible.

The resistance to inflation may be high especially when significant broncho-spasm, pneumonia, left heart failure, or pulmonary fibrosis are present. Thoracic wall compliance may be low and, when marked distress exists, tachypnoea may further hamper ventilation. Patient-triggered respiration, set at pressures which produce adequate tidal volumes, may slow the rate. However, if the slowing is insufficient to prevent trapping, small doses of intravenous narcotic may be beneficial. If this is ineffective, or when it produces hypotension, one may paralyse the patient with muscle relaxant. This is a serious and somewhat retro-grade step and, although used in four instances in the present series, its necessity is of grave prognostic import. In all cases, ventilation will be improved by the efficient aspiration of secretions, which may be assisted by the use of broncho-dilators and vasoconstrictors delivered by nebulizer.

Essentially, the management of emphysema involves vigorous and meticulous routine measures, with ventilatory assistance where death could result without it. This description does not refer to cases of emphysema in which I.P.P. is used solely as a means of delivering nebulized medications to the bronchial tree.

Three different methods of giving assisted respiration in emphysema have been assessed recently, I.P.P. being preferred to tank and cuirass respirators (122).

Management of Post-Operative Respiratory Insufficiency

Patients unable to breathe following surgery fall into two broad groups: (i) those with temporary, easily reversible problems such as persistent curariza-tion, excessive cental depression, either by general anaesthesia or by narcotics, pneumo-thorax, haemothorax, atelectasis, and so on, and (ii) those with states considerably more resistant to correction. It is with the second group that we are primarily concerned. These patients almost always have some form of pre-existing respiratory defect to which the effects of surgery are added. Another group are those who have undergone neurosurgery or sustained head injuries with resulting damage to respiratory pathways and who may be treated in the same way as any other central nervous system lesion (123).

The limitations imposed by surgery are those of pain in the abdomen and thorax, tight dressings, abdominal distension, and various intrathoracic disorders. Among the latter, disorder of thoracic wall movement following thoracotomy, broncho-pneumonia, and atelectasis are well recognized. Changes in pulmonary

function following thoracotomy and I.P.P. have been described and the deterioration in diffusion emphasized (17). Distribution is also said to be impaired and, following muscle relaxants, the decreased thoracic and, hence, lung volume is said to lead to poor expansion and perfusion in peripherally placed lobules. This obviously depends upon many variables.

One group which has not received attention in the literature includes those with poor thoracic movements because of age, debility, toxicity, and so on. It has been noted that these patients behave very like those with muscular weakness produced by poliomyelitis or myasthenia, for example. Thus, after relatively good respiratory efforts for a period, they may quickly become exhausted and even apnoeic.

Essentially, the treatment consists of tiding the patient over until the limitations added by surgery resolve. In the absence of an obviously reversible complication, the patient with a chronic respiratory disorder, breathing inadequately after surgery to chest or abdomen, will usually require several days respiratory assistance. Early recognition of this situation is therefore important. Repeated failed trials of spontaneous respiration frequently change a mild to a serious situation as a result of recurrent bouts of hypoxia and hypercarbia.

Features peculiar to cardiac surgery. Pulmonary lesions occurring after cardiac surgery frequently produce hypoxia and the need for adequate oxygenation is paramount. The myocardium and its conduction mechanism are extremely sensitive to hypoxia at this stage.

Many patients with the respiratory embarrassment of chronic left heart failure pass through the first few post-operative days on the brink of respiratory insufficiency. Inability to cough up secretions frequently necessitates tracheostomy with or without I.P.P.

Following surgery for conditions associated with pulmonary hypertension—mitral valve disease, atrial and ventricular septal defects—and especially when extracorporeal circulation is used, respiratory insufficiency is among the most common causes of death. This appears to occur in two forms: (i) diffusion defects without copious sputum and without marked clinical or radiological evidence of changes in the lung fields. Such patients benefit from 100 per cent oxygen, administered via tracheostomy by I.P.P., and (ii) the respiratory insufficiency syndrome, characterized by patchy pulmonary congestion, copious sputum, severe respiratory distress, and rapid progression to death. While this can be avoided to some extent by selection of patients and by extracorporeal technique, once the situation has arisen its course can often be reversed by I.P.P.

Whatever the cause, any increased work of breathing may be dangerous in a patient with a damaged myocardium and, in this group, ventilatory assistance should be considered early. Tachypnoea and high total resistance may indicate the use of relaxants and a volume-constant machine. An occasional indication for assisted ventilation occurs when deficient respiration prevents adequate compensation for metabolic acidosis. This has been seen in pneumonia accompanying gross oliguria and is not uncommon following cardiac surgery, particularly when hypothermia or extracorporeal circulation have been used.

Management of Pneumonia

In our experience, pneumonia has led to ventilatory insufficiency in the following circumstances: (i) as a complication of pre-existing respiratory disease, for example, emphysema; (ii) post-operatively; (iii) in staphylococcal pneumonia; and (iv) when coexisting with metabolic acidosis.

Carbon dioxide retention is relatively rare in pneumonia but each of the first two groups has added reason for hypercarbia. Those patients with staphylococcal pneumonia have developed serious trouble due to crusting of secretions within the bronchial tree. Certain points are significant:

(*a*) *Oxygenation*. This group causes great anxiety in this regard. Venous admixture, poor diffusion, and, in many instances, disturbances in distribution all lead to low arterial O_2 tension without CO_2 retention. In fact, the tachypnoea of pneumonia may produce hypocarbia. Oxygen must be added to the inflation gases in quantities adequate to produce an oxygen saturation as near normal as possible.

(*b*) *Tachypnoea*. The extreme tachypnoea sometimes seen may limit tidal volume to an extent where alveolar ventilation falls. Intravenous narcotics may prove helpful, but in extreme cases muscle relaxants may be required. The tachypnoea may produce exhaustion and death, and is an indication for early assisted ventilation.

(*c*) *Resistance to ventilation*. This is raised and ventilators with high maximum pressures may be required to ventilate patients with extensive disease. Experience has shown that even in gross multilobar consolidation adequate ventilation can be achieved by such equipment.

(*d*) *Bronchoscopic equipment*. Emergency bronchoscopy has become a very rare procedure in the Toronto General Hospital unit, with the exception of staphylococcal pneumonia, where plugs too large for suction equipment may have to be removed with grasping forceps. This is particularly liable to occur when the tracheo-bronchial mucosa is destroyed by infection, as in post-influenzal pneumonia.

Management of Stove-In-Chest

The use of I.P.P. in stove-in-chest has revolutionized its management (78). Death from asphyxia is prevented, pain is controlled, and mechanical devices to support the thoracic cage are eliminated, as the chest wall is uniformly supported by the intermittent intrathoracic positive pressure.

While conservative management is satisfactory in certain of these cases, this will usually be the exception when paradoxical movement of the chest wall occurs. Shortly after injury only relatively minor degrees of paradox may be present but, uncorrected, this is sometimes progressive and leads to gradual deterioration. We have twice seen neglect of such minor degrees of paradox lead to death from cardiac arrest.

The immediate requirements are to secure an airway and to control ventilation. The patient is intubated, usually under general anaesthesia, and ventilation is begun. Control is achieved by overventilation until respiratory alkalosis is

sufficient to remove the CO_2 stimulus to spontaneous respiration. This may be expedited by one dose of muscle relaxant at the outset. The degree of over-ventilation is adjusted to the point where any reduction in minute volume is followed by spontaneous respiratory efforts. Oxygen in percentage higher than that in room air may be required. No advantage has been found in using uncuffed tubes and any machine capable of delivering stroke volumes up to 1 L. may be used satisfactorily with cuffed tubes.

When satisfactory ventilation is secured, other conditions are searched for and dealt with (124). Air or blood in the pleural or pericardial cavities, gastric dilatation and paralytic ileus, abdominal injuries, head injuries, whip-lash injuries, and fractures and dislocations around the shoulder girdle are common. An ECG will often reveal evidence of myocardial injury, sometimes with an associated atrial arrhythmia. A chest X-ray should be taken as early as possible and usually shows extensive pulmonary mottling due to intrapulmonary haemorrhage.

When ventilation has been established and the patient examined, and when other conditions have been dealt with and the patient's general condition improved by transfusion and whatever other measures are needed, tracheostomy is done.

These patients are nursed on a ripple-mattress in a semi-sitting position and are the exceptions to the rule that those needing artificial respiration are turned frequently. Turning is very painful and delays union.

The presence of intra-alveolar blood is taken as an indication for prophylactic antibiotic therapy. Such patients are pyrexial and the onset of infection is difficult to detect. Other conditions arising from this type of injury are dealt with on their merits, irrespective of the need for assisted respiration.

The chest becomes stable in from 10 to 30 days, depending largely on the severity of the injury and the age of the patient. I.P.P. should be continued until paradox is absent or very minimal, or some deformity of the chest wall will result.

Transportation of Patients with Respiratory Insufficiency

Patients with respiratory inadequacy have travelled all over the world, assisted by cabinet respirators or I.P.P. The latter lends itself particularly well to this purpose, as the equipment does not require much space and is easily portable.

For transportation, one requires a clear airway, suction equipment, and a method of applying I.P.P.

(*a*) *Airway.* Endotracheal intubation remains the method of choice, requiring only simple equipment readily available in most hospitals. Adequate topical anaesthesia at the outset and subsequent administration of sedation and cough depressants render the tubes tolerable.

It has been suggested that intubation may convert a "dry" to a "wet" chest (125). This has not been our experience, although marked salivation and bronchial secretion occur in association with distress and objection to the tube. Adequate

sedation, topical anaesthesia, and efficient suction have proved satisfactory in avoiding this.

(*b*) *Suction equipment.* Portable equipment may be obtained which runs off compressed air, D.C. battery, or foot pump. Catheters for use with endotracheal tubes should be longer than ordinary urethral types and special endobronchial suction catheters are available. In their absence a shortened duodenal tube may be better than a urethral catheter.

(*c*) *I.P.P. equipment.* For short periods, a bag and non-return valve may be used with a source of oxygen. Alternatively, a self-inflating bag may be used with air. For longer journeys, mechanical respirators are available, working from D.C. batteries.

The practice of transporting a patient with inadequate respiration with an unsecured airway and no means of ventilation or suction is very dangerous.

Results of Treatment

This article is concerned with a discussion of method. For this reason and because, with some notable exceptions, the numbers of cases of any one condition yet reported are small, a detailed consideration of prognosis would be out of place. This section will, therefore, be confined to a discussion of the results in 100 consecutive admissions to the Respiratory Unit of the Toronto General Hospital. (See Table I.)

The first consideration in assessing results is the selection of cases. This has depended in the first place on the referring physician. In general, the cases that have been referred have been ones of underventilation as a result of disorders that carry a fairly good prognosis and ones of undiagnosed disease, not those resulting from progressive and mortal illness or from illness that directly destroys the mind and personality. Hence, if the patient can be tided over the period of underventilation, the prognosis is that of the primary condition and is not altered by the fact that artificial respiration has been necessary. The possibility that a patient will never become free of the need for respiratory assistance is often present, of course, and of the 75 survivors, one, a myasthenic, needs help from the rocking bed for some part of each day.

Emphysema is to some extent a special case in that the fundamental lesion is progressive. In common with all who have treated cases of emphysema in this way, we have been impressed by the difficulty of predicting the outcome once the need for respiratory assistance is over. In some, we have been surprised by the improved and relatively excellent health of the patient; in others there has been no significant improvement. We have not found it possible to predict into which category any given patient would fall.

With the exception of patients with neurological disease, in whom the possible need for artificial respiration has long been stressed, the use of these techniques is relatively unfamiliar. Hence, patients are often not referred until they are thought to be dying. While it is true that artificial respiration is hazardous and not to be entered into lightly, and that skilful management of those on the brink

of underventilation will sometimes avoid the necessity for its use, it is no less a part of skilful management to institute artificial respiration before an urgent situation has become desperate.

The causes of death are set out in Table I. The largest group, the patients with emphysema, were considered above. Of the patients with cardiac arrest, three followed cardiac surgery; one was the consequence of not giving I.P.P. to a patient with a stove-in-chest and the other was the result of intracranial haemorrhage.

TABLE I

	Diagnosis	Treated	Survived	Died	Cause of death
Neurological disorders					
Central	Drug intoxication	16	15	1	Anoxia
	Intracranial aneurysm	1	0	1	Cardiac arrest
	Anoxia from drowning	1	0	1	G.I. haemorrhage
	Disseminated sclerosis	2	2	0	
	Cervical cord injury	5	4	1	Haemorrhage, traumatic
Peripheral	Myasthenia gravis	7	6	1	Haemorrhage, secondary
	Peripheral neuropathy	4	3	1	Pneumonia
	Poliomyelitis	1	1	0	
	Hyperpotassaemic paralysis	1	0	1	Renal failure (subac. glomerulonephritis)
Curare	Status epilepticus	3	2	1	Anoxia
	Tetanus	1	0	1	Pneumonia
Emphysema		23	15	8	
Post-thoracotomy	Cardiac	9	5	4	Cardiac arrest—3 Renal failure (following shock)—1
	Pulmonary	1	1	0	
Post-laparotomy		8	6	2	Peritonitis
Chest Injury	Stove-in-chest	8	7	1	Cardiac arrest
	Gunshot wound	2	1	1	Pneumonia
Miscellaneous	Status asthmaticus	1	1	0	
	Post-influenzal pneumonia (Staph. aureus)	1	1	0	
Observation	Need for I.P.P. avoided	5	5	0	
		100	75	25	

Three patients died of pneumonia and in two of them the infection might be counted as a failure of the technique of treatment.

Cerebral anoxia was the cause of status epilepticus in two cases admitted for this condition and resulted in the death of one. Another case of anoxia was due to hypotension, prior to admission to hospital, from an overdose of seconal.

Haemorrhage from the denuded mucosal surface of the upper gastro-intestinal tract, resulting from ingestion of carbolic acid, was the cause of death in the patient admitted following a double attempt at suicide, by poisoning and drowning. The other cases were due to rupture of the spleen and to secondary haemorrhage following thymectomy.

Of the survivors, about whom information is available, the great majority are back at their normal occupations. In three patients it has not been possible to close the tracheostomy. Two, one with poliomyelitis, and one with myasthenia gravis, have persisting bulbar palsy. The first is working at the job he had before his illness, the second is still in hospital needing periods of assisted respiration.

The third, with emphysema, leads a contented life of retirement. Those who have not returned to their usual occupations are the cases of disseminated sclerosis and of cervical cord injuries. These patients have followed the course usual in those conditions and have done perhaps rather better than most. Other than the two patients with granulomata of the vocal cords referred to above, no *sequelae* attributable to I.P.P. have been observed.

SUMMARY

The management of patients with respiratory insufficiency, using intermittent positive pressure, has been discussed in detail. Emphasis has been laid on the underlying physiological problems and on the need for detailed specialized knowledge.

The available equipment and methods of use are discussed, together with methods of monitoring assisted respiration. Problems of diagnosis of underventilation, general principles of management and the problems associated with the more common causes of respiratory insufficiency are discussed.

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BOOK REVIEW

ESSAYS ON THE FIRST HUNDRED YEARS OF ANAESTHESIA. Vol. I.
By W. Stanley Sykes, M.B.E., M.B., B.CHIR., D.A.
Toronto: The Macmillan Company of Canada Ltd. 1960. $5.00.

DR. SYKES' APPROACH to anaesthesia is that of a biographer to a hero or heroine whom he has known and admired, whose life he wished to record faithfully. The enthusiasm of the author for his subject is evident on every page, carrying the reader effortlessly from chapter to chapter. Interesting information, dug out of time-tables and old medical journals, brings a liveliness to the history by showing personalities against the background of their times. The author's choice of illustrations is delightfully unexpected, as, indeed, is the character of the whole account. It is to be hoped that Volume II will carry on in the same pleasant, humourous, and informative style.

S.A.F.

NEWS LETTER

DR. ALLEN B. DOBKIN, Associate Professor of Anaesthesia at the University of Saskatchewan, has been appointed Professor of Anesthesiology at the Upstate Medical Centre of the University of Syracuse, New York. Dr. Dobkin will assume his new duties in the fall.

Dr. John H. Harland has resigned his appointment of Instructor in Anaesthesia at the University of Saskatchewan to enter private practice in August with the Underhill Clinic in Kelowna, B.C.

Dr. F. C. Haley, formerly Instructor of Anaesthesia at the University of Saskatchewan, has been appointed Assistant Professor of Anaesthesia at the University of Alberta, Edmonton, Alberta, effective August 1, 1960.

Dr. A. M. Keil has relinquished his appointment as Instructor of Anaesthesia at the University of Saskatchewan on September 30 to join the Anaesthetic Associates at Calgary, Alberta.

Dr. C. J. Kilduff, formerly Instructor of Anaesthesia at the University of Saskatchewan and in recent years in private practice in Saskatoon, has re-joined the full-time staff at the University Hospital, Saskatoon and has been appointed Assistant Professor in the College of Medicine effective July 1, 1960.

Dr. A. R. Boutros, late Senior Clinical Fellow in Anaesthesia at the Royal Victoria Hospital, Montreal, has been appointed Instructor in Anaesthesia at the University of Saskatchewan where he assumed his duties on July 1, 1960.

Dr. H. V. Donaldson has completed one year as Research Fellow in Anaesthesia at the University of Saskatchewan and has joined the Anaesthetic Services of Calgary, Alberta, on July 1, 1960. His position as Research Fellow has been taken over by Dr. C. A. Chang, hitherto a Clinical Fellow in Anaesthesia at the University Hospital, Saskatoon.

Dr. A. W. Conn has been appointed Anaesthetist-in-Chief to the Hospital for Sick Children, Toronto, on the retirement of Dr. C. I. Junkin.

CANADIAN ANAESTHETISTS' SOCIETY JOURNAL

Volume 7

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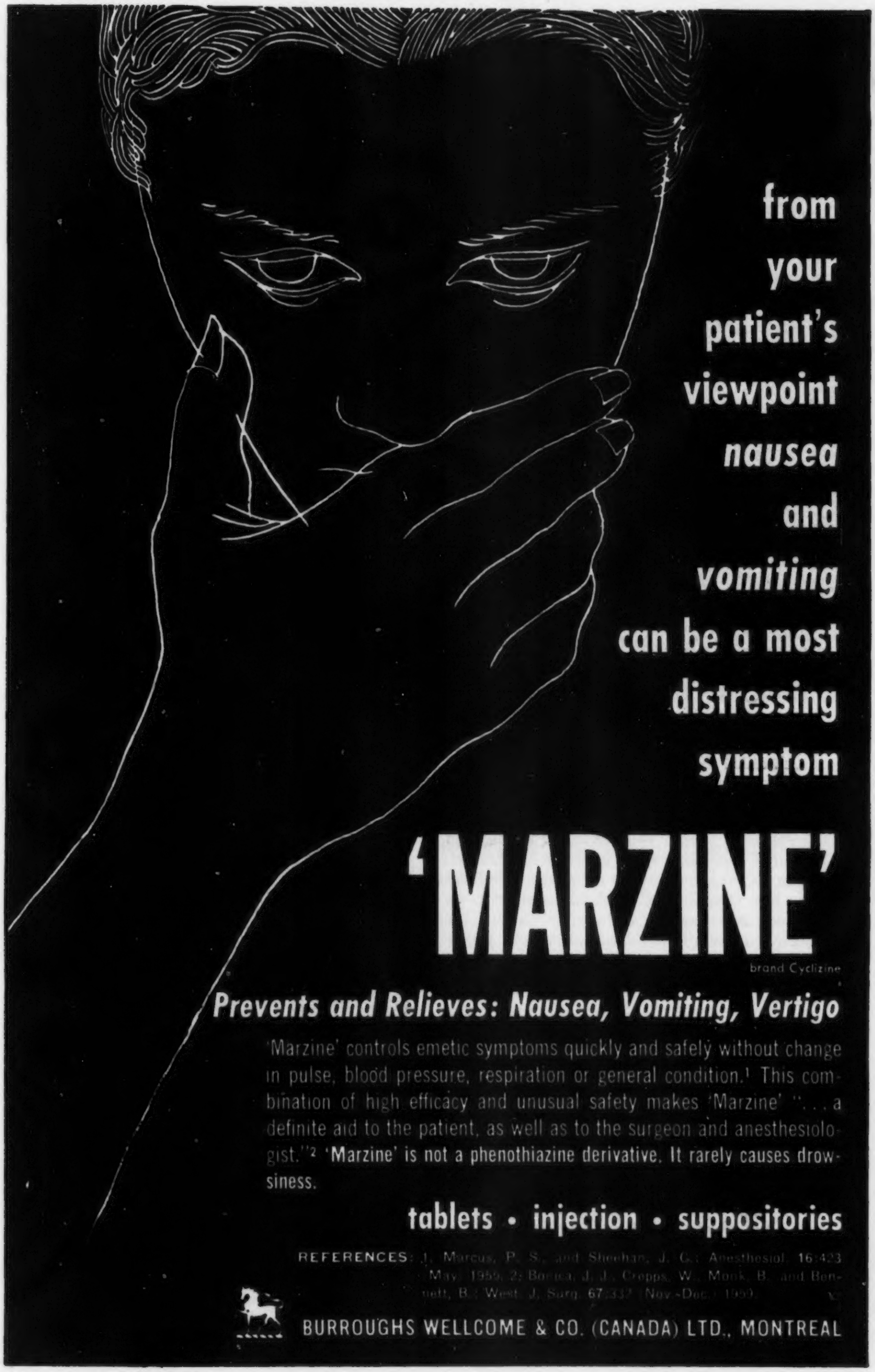
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